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Archives of Internal Medicine

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RESUSCITATION OF THE STOPPED HEART BY INTRACARDIAC THERAPY *

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No procedure in modern medicine has aroused more controversial thought than the attempt to revive the dead. Hailed on the one hand as a miracle of science and on the other as a useless and dangerous operation,[1] the intracardiac injection method of resuscitating the stopped heart has occupied a stage of excited debate.

The dramatic circumstances attending the revival of those supposedly dead readily lends itself to exploitation by both the lay and the medical press. The subject is naturally one of appealing interest, touching as it does on two fundamental concepts of philosophic thought—life and death.

The increasing use of epinephrine for intracardiac injection in emergency conditions arising in the operating room and in the physician's office has been attended with such inconstant results that many surgeons and physicians are at a loss in evaluating the efficacy of this procedure, individual experience having rendered them either enthusiastic advocates or bitter opponents of this method of resuscitation.

In spite of the frequent isolated reports rendered by many authors who have published results of cases in which the patients were treated by intracardiac therapy, the literature contains no systematic study of this problem, and the physician is left confused and not a little bewildered by the loosely worded speculative thought which is often expressed in these cases.

Sensing the need of scientific inquiry into all phases of intracardiac therapy, the Witkin Foundation in 1926, created a special committee to investigate this problem. Through the philanthropic magnanimity of Mr. Witkin, funds were made available for the study of the various questions arising in the procedure of intracardiac manipulation. A correlation of results obtained from the laboratory, clinic and hospital

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* Report of the Special Committee on Intracardiac Therapy of the Witkin Foundation.

1. Editorial: Resuscitation and Intracardiac Injections, J. A. M. A. **94**:107 (Jan. 11) 1930.

in the four year period from January, 1926, to January, 1930, constitutes the source from which this report is made.

HISTORICAL DATA

The intracardiac route for the injection of drugs into the circulation received prominent attention at a symposium held in Munich in 1921. Guthman,[2] Vogt [3] and Frenzel [4] reported their experiences in the use of epinephrine injected into the heart when complete asystole developed during the course of surgical anesthesia. Up to that time, there had been collected from the literature twenty successful cases from seventy-six patients who had been treated by this method.

Prior to 1921, there were isolated reports in regard to the intracardiac route of injection; Vanden Veldin [5] is said to have used this method as early as 1909. Fantus [6] said that the German physiologist Schiff discovered this method of approach to the failing heart more than fifty years ago.

Boden,[7] in 1923, had collected ninety cases with favorable results reported in twenty-three; most of these patients had received intracardiac injection of epinephrine for asystole of the heart occurring during operative procedures performed under general anesthesia. The literature since that time contains more and more reports of intracardiac injections used for resuscitation of the stopped heart.

Meyer,[8] Raeschke,[9] Petzetakis,[10] Garipuy and Mériel,[11] O'Donovan and Fitzpatrick [12] and Sellheim [13] contributed observations made during the attempt to reanimate the asystolic heart by the injection of epinephrine into the circulation. The success of their efforts led to an investigation into its possible use for the development of the circulation in stillborn infants. In 1926, Wachenfeldt [14] and Bardier [15] were able to resuscitate new-born infants when all other measures had failed; the injection of epinephrine directly into the heart met with favorable results.

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2. Guthman, C.: München. med. Wchnschr. **68**:729 (June 17) 1921.
3. Vogt, E.: München. med. Wchnschr. **68**:732 (June 17) 1921.
4. Frenzel, B.: München. med. Wchnschr. **68**:730 (June 17) 1921.
5. Van den Veldin, quoted by Vogt, E.: München. med. Wchnschr. **68**:732, 1921.
6. Fantus, B.: The Technic of Medication, J. A. M. A. **87**:563 (Aug. 21) 1926.
7. Bodon, C.: Lancet **1**:586 (March 24) 1923.
8. Meyer, C.: Jahrb. f. Kinderh. **107**:76 (Sept.) 1924.
9. Raeschke, G.: Zentralbl. f. Chir. **51**:1628, 1924.
10. Petzetakis, M.: Presse méd. **34**:84 (Jan. 20) 1926.
11. Garipuy and Mériel: Presse méd. **34**:180 (Feb. 10) 1926.
12. O'Donovan, J. S., and Fitzpatrick, J. D.: Brit. M. J. **2**:524 (Sept. 18) 1926.
13. Sellheim, H.: Med. Klin. **22**:1323 (Aug. 27) 1926.
14. Wachenfeldt, M.: Monatschr. f. Geburtsh. u. Gynäk. **72**:185 (Feb.) 1926.
15. Bardier, E.: Bruxelles-méd. **8**:1242 (July 22) 1928.

Within the past three years, there have been reported sixty-two other cases in which the intracardiac injection method of resuscitation has been employed; these reports, together with those previously mentioned, make a total of about 250 cases in about 25 per cent of which a favorable outcome was experienced.

WHAT IS MEANT BY INTRACARDIAC INJECTION

A brief study of the cases reported by various authors quickly reveals the great confusion existing in regard to the procedure called "intracardiac injection." With the exception of obscure references made in regard to the left ventricle, few investigators have even attempted to indicate specifically which part of the heart or adjacent structures they were attempting to reach by the injecting needle.

From a purely anatomic point of view, there are three sites that can be considered in the all-inclusive phrase "intracardiac injection": (1) the pericardium, (2) the wall of the heart and (3) the cavities of the heart.

Of these three sites, the attempt to inject substances into the cavities of the heart, and especially that of the left ventricle, was apparently the intent of many authors. The rationale of this thought seems to be based on the theory that with the heart at standstill the intravenous route of medication is ineffective, but if the injected drug reaches the heart immediately, it may be carried without delay to the easily perishable centers of the brain. Furthermore, injection directly into the left ventricle saves the time required for passage through the lesser circulation and hence enhances the chances of the injected material to reach the brain and other "vital centers" more quickly.

A consideration of this conception of intracardiac therapy would seem to show, however, that it is based on a fallacious theory; it is obvious that if the heart is at a standstill there will be no more circulation within the cavities of the heart than there will be in the venous or arterial circulation. One cannot accept the favorable results noted in resuscitation of the asystolic heart on the fact that the injected drug is placed more quickly into circulation.

Injection of the drug into the wall of the heart has been the intent of several more careful observers. Their conception of the process is based on certain facts demonstrable in the experimental laboratory; the isolated mammalian heart may be stimulated to automatic contraction after a period of standstill when epinephrine and other substances are injected into the myocardium. The local effect of epinephrine on the heart muscle has been widely studied by many investigators; the increase in the capillary circulation makes possible a quicker metabolic exchange in the myocardial fibers with a resulting renewal of automatic contrac-

tion. Other substances, when injected into the myocardium of such laboratory heart preparations will also cause a renewal of rhythm after standstill.

In attempts to resuscitate the stopped heart, injections into the pericardial cavity apparently have not been made intentionally. This, however, has been done inadvertently several times during attempts to inject substances into the heart. Failure to use needles of sufficient length, incorrectly placed needles and injections made before the needle had passed into the heart itself have been responsible for the injection of substances into the pericardial cavity. Neureiter [16] had an opportunity to examine several subjects that had received "intracardiac injection" in the attempt at resuscitation; at the postmortem table he found that the injected material was in the pericardial cavity in two cases, and from a pathologic point of view no specific reaction could be discovered. Apparently, the injection of substances into the pericardial cavity has little or no effect on the heart at standstill.

A review of these facts would thus tend to indicate that as far as resuscitation is concerned, the procedure of injection into the heart seems to be most effective when the drug is placed in the heart muscle; it is very much less effective when injected into the cavities of the heart, and it apparently has no value when injected into the pericardial cavity.

DRUGS USED IN INTRACARDIAC INJECTIONS

While epinephrine has enjoyed widespread use as the drug *par excellence* for use in cardiac standstill, many authors have shown that this substance may not be used without great danger. Johnson and Siebert [17] demonstrated that severe myocardial damage occurred in nearly all of their forty-seven animals that had been used in the study of this problem. Hume,[18] Smirnow,[19] and Lucchetti [20] have also shown that there may be extensive cardiovascular involvement following the use of epinephrine, more especially when it is injected during anesthesia. Neureiter [16] confirmed many of these observations from autopsy material.

Many other drugs have been used for the resuscitation of the arrested heart. Bolton [21] was successful in restoring contraction of the heart by the intracardiac injection of ether; in his case, the heart

16. Neureiter, F.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **12**:151 (Aug. 27) 1928.
17. Johnson, S., and Siebert, W. J.: Am. Heart J. **3**:279 (Feb.) 1928.
18. Hume, W. E.: Quart. J. Med. **21**:459 (July) 1928
19. Smirnow, A. J.: Ztschr. f. d. ges. exper. Med. **57**:554, 1927.
20. Lucchetti, Prat. méd. franç. **6**:113 (March) 1927.
21. Bolton, N. H.: Brit. M. J. **2**:482 (Sept. 11) 1926.

responded promptly to the injection when all of the usual methods of reanimation had failed.

Caffeine has been used with favorable results by several investigators. Bianchetti [22] injected relatively small amounts in his case, while Wiechowski [23] tried huge doses of the drug; both authors were equally enthusiastic about its immediate action in moribund patients, one of them having been dead for about twelve minutes.

Dextrose was first used by Imerman;[24] he injected 10 cc. of a 20 per cent solution of dextrose directly into the heart of a patient suffering from insulin shock. With the patient apparently dead, the response to the intracardiac injection was prompt, and subsequent recovery occurred rapidly.

Sodium thiosulphate was utilized in an attempt to save a patient who had tried to commit suicide by taking a large amount of potassium cyanide; with the patient moribund, Zimman [25] injected this chemical directly into the left ventricle, with a favorable outcome. He reported no untoward results from the injection.

Many combinations of substances have also been used for intracardiac injection; Ronzini's solution [26] is probably the best known of this group. This solution contains epinephrine, atropine, pituitary extract, and lobeline and is injected in doses of from 2 to 4 cc.

Camphor, digitalis, strophanthin, metrazol, coramin, strychnine and hypertonic salt solution, either alone or in combination with each other and epinephrine, have been used for intracardiac injection. Vogt [3] studied the effect of many of these substances, and his conclusion seemed to be that all of them are more or less valuable for resuscitation of the asystolic heart.

The wide variety of substances used for intracardiac injection suggests that the response of the heart is probably not specific to any pharmodynamic action, but that other factors, to be discussed later, are responsible for the resuscitation of the heart.

MECHANICAL STIMULATION OF THE HEART

Accidental standstill of the heart is not an unfamiliar occurrence in the surgical amphitheater; this unfortunate experience can be related by every practicing physician. The attempt to resuscitate the heart by direct or indirect manipulation has been practiced during such emer-

22. Bianchetti, C. F.: Riforma med. **42**:498 (May 24) 1926.
23. Wiechowski, W.: Wien. klin. Wchnschr. **41**:475 (April 5) 1928.
24. Imerman, S. W.: Intracardiac Injection of Dextrose in a Case of Insulin Hypoglycemia, J. A. M. A. **89**:1778 (Nov. 19) 1927.
25. Zimman, J.: Semana méd. **1**:1235 (May 17) 1928.
26. Ronzini, M.: Policlinico **35**:90 (Feb. 15) 1928.

gencies for at least the past seventy-five years, and the literature contains many reports of the favorable results obtained by this method.

When the emergency has developed during the course of a laparotomy, the surgeon has attempted to massage the heart by direct pressure on the diaphragm; squeezing, pinching or otherwise mechanically irritating the heart to recontract has been the theory behind such procedures (Cook [27]). Indirect methods of cardiac massage by pressure applied on the thorax have often been resorted to. Krantzfeld [28] recently reviewed the various methods of mechanically stimulating the heart in such cases. Many devices and machines have also been devised to accomplish the same purpose.

Condorelli [29] described a case in which he kept the heart beating for more than two hours by thumping on the precordium; every time the heart was percussed a contraction occurred, but when the percussion was stopped the heart would immediately cease contracting, and the patient would become unconscious and moribund. The impossibility of continuing this procedure resulted in the death of the patient.

Eisenmenger [30] described a pumping apparatus which is applied to the abdomen; this device consists of a small motor which alternately massages the abdomen while a pump forces sodium chloride solution into the blood vessels. With this machine he was able to maintain a circulation in patients who had died; if the apparatus was used not more than ten minutes after cardiac standstill, favorable results might be expected. The machine, however, is so complicated that it has been difficult to make use of it clinically; Eisenmenger has therefore been devoting his attention to demonstrating the chemical changes that take place in the body during the time that artificial circulation has continued. His picturesque description of corpses that regain natural color and bodies that continue to show automatic movements has recently challenged the credulity of all Europe.

While the mechanical methods of resuscitating the asystolic heart still enjoy considerable vogue, the widespread attention given to the intracardiac injection procedure has made the latter method the one more widely used at the present time, so that the reports now appearing in the literature are concerned less and less with the mechanical theory of reanimating the stopped heart.

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27. Cook, L.: Brit. M. J. **2**:1118 (Dec. 11) 1926.

28. Krantzfeld, I.: Klin. Med. **5**:808 (Aug.) 1927.

29. Condorelli, L.: Minerva M. J. **8**:343 (Aug. 18) 1928.

30. Eisenmenger, R.: Trials with Mechanical Artificial Breathing (Letter), J. A. M. A. **94**:121 (Jan. 11) 1930.

THE RESUSCITATION PERIOD

Physiologists have long maintained that a sudden stopping of the circulation results in an unequal response on the part of different tissues of the body. Certain centers of the brain are apparently quickly effected, while simple glandular structures like those of the hair follicles in the skin have been demonstrated to exhibit signs of activity even seventy-two hours after the heart has stopped beating. The easily perishable centers of the brain, however, are said to be irreparably damaged after from five to eight minutes of cerebral anemia.

The question as to how long asystole of the heart may exist and yet be responsive to intracardiac therapy apparently bears no relation to the physiologic thought previously expressed. Many cases of cardiac arrest have been reported which have greatly exceeded the maximum of eight minutes laid down by the experimental physiologist.

The period during which resuscitation may be possible has been found by different authors to be as long as from fifteen to twenty minutes, the longest case being that reported by Truzzi,[31] in which a man, aged 70, was effectively treated by intracardiac injection more than half an hour after all signs of cardiac activity had ceased. Kleinberg[32] recorded a case in which the patient was successfully treated twenty minutes after standstill of the heart; his patient was unquestionably dead before intracardiac therapy was resorted to. Johnson's[33] patient was a child, who was resuscitated twelve minutes after apparent death; Lutand's[34] patient recovered after ten minutes of cardiac standstill.

To these cases may be added two of our own; one, that of a man, aged 36, with cardiac arrest while on the operating table. Epinephrine injected into the heart eleven minutes afterward caused prompt recovery. The other case was that of a child who suffered from asystole of the heart during tonsillectomy; fourteen minutes after apparent death, 3 cc. of metrazol was injected into the left ventricle with a favorable result, the child showing no untoward results.

To describe the interval during which restoration of cardiac activity may be possible, we have used the phrase "resuscitation period." This period seems to be much longer than that previously conceived, and further experimental study is required to determine what its actual duration may be in relation to the various factors of age, sex, anesthesia, shock, hemorrhage and disease.

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31. Truzzi, E.: Gazz. d. osp. **49**:1507 (Nov. 25) 1928.

32. Kleinberg, S.: Pulmonary Embolism Following Oxygen Injection of a Knee, J. A. M. A. **89**:172 (July 16) 1927.

33. Johnson, G.: Norsk mag. f. laegevidensk. **89**:478 (May) 1928.

34. Lutand, P.: Bull. et mém. Soc. de chir. de Paris **20**:874 (Dec. 21) 1928.

Sufficient facts are at hand, however, to indicate that some attempt should be made to reestablish cardiac activity even if there has been a long period of cardiac arrest; if the procedure of injection is performed in the manner to be described later, a favorable outcome may be expected in cases in which the patients might otherwise have succumbed.

INDICATIONS FOR INTRACARDIAC INJECTIONS

Any procedure fraught with so many sequela, both good and bad, must be intelligently understood before its performance is undertaken: a consideration of the use of intracardiac injections must be made to determine the indications and contraindications in its selection as a method of resuscitating the stopped heart. Widespread utilization and poorly selected cases have done much to discredit this mode of reanimating the asystolic heart.

As long ago as 1924, Meyer [8] suggested that all hearts in which cardiac arrest has occurred could be divided into two groups: (1) the healthy asystolic heart and (2) the heart in acute or chronic disease.

In the first group may be placed the heart that stops under narcosis, anesthesia, shock, accidents, injuries and collapse; while in the second group may be placed hearts suffering from those cardiovascular conditions leading to or associated with decompensation or general vasomotor breakdown. To the second group Vogt [3] added arterial sclerosis, muscular degeneration of the heart, hyperthyroid disease with cardiac complications and nephrosis. Van den Velden [5] thought that collapse from the acute infectious diseases should be considered; Hesse [35] suggested the incorporation of peritonitis from perforations, epidemic meningitis, diphtheria, pneumonia, pulmonary tuberculosis, typhus and typhoid. Finally, Blau [36] added poisoning by chemicals or gases.

A review of these conditions suggests that intracardiac injection should be more effective in the first than in the second group. There can be no question that when the heart is normal and unaffected by disease process in itself or in other parts of the body, the efficacy of this method of resuscitation must be much better than in the other group. This is readily borne out by an analysis of the successful cases that have been reported in the literature; most, if not all, of these have been made of cases appearing in the first group. The unsuccessful and poor results have been found almost exclusively in the second group, and it has been in the latter group that most of the serious complications, like hemopericardium, pericardial infection, embolism and general septicemia, have occurred.

35. Hesse, quoted by Meyer, C.: Jahrb. f. Kinderh. **107**:76 (Sept.) 1924.

36. Blau, J., quoted by Meyer, C.: Jahrb. f. Kinderh. **107**:76 (Sept.) 1924.

Intracardiac injection should be reserved, therefore, with few exceptions, for the normal healthy heart that has stopped for the reasons enumerated in group one. To these, however, may be added another group of conditions occurring in childhood and infancy which seem to be peculiarly responsive to this method of therapy—asphyxia of the newly born or premature infant, thymic death and collapse from chronic nutritive disorders.

Occasionally, intracardiac therapy may be indicated in serious decompensation of the heart when all other methods of administering drugs are ineffective. Schultze[37] reported a case in which a girl, aged 7 years, was given fifteen intracardiac injections of strophanthin with successful results. We have used a digitalis product by the intracardiac route three times with a favorable outcome in one case.

In selecting cases for intracardiac injection in the hope of restoring cardiac activity, attention must thus be paid to the general condition of the patient. When the patient is suffering from serious systemic disease and when the heart has stopped as the result of myocardial degeneration, it is obvious that such cases are unsuited for intracardiac attempts at resuscitation; failure will be the rule.

On the other hand, when a patient is undergoing a surgical operation or when shock and injury have rendered an otherwise normal person moribund as the result of cardiac arrest, the intracardiac mode of stimulating automatic contraction of the heart should be attempted, as this procedure offers a favorable outcome if performed in a satisfactory manner.

PRESENT STATUS OF INTRACARDIAC THERAPY FOR RESUSCITATION OF THE STOPPED HEART

From the foregoing data, the present status of intracardiac injection for reviving the stopped heart may be summarized briefly as follows:

1. A sufficiently large number of persons have been resuscitated after apparent death by the use of intracardiac injections to make this method worthy of further study.

2. Considerable confusion exists in regard to the procedure called "intracardiac injection," little if any attempt being made to determine the actual site of the injection—whether pericardial, myocardial or into the chambers of the heart itself.

3. From an experimental point of view, the procedure is unquestionably more effective when the drug is injected into the heart muscle alone, and least effective when it is placed in the pericardial cavity.

37. Schultze, M., quoted by Meyer, C.: Jahrb. f. Kinderh. **107**:76 (Sept.) 1924

Injections into the cavities of the heart appear to rank in effectiveness about half way between these two.

4. The procedure is more successful in the normal asystolic heart (group 1) than in hearts suffering from disease processes (group 2).

5. While epinephrine has been used most often, there is a wide selection of drugs that has proved to be effective in the resuscitation process.

6. The resuscitation period apparently bears no relation to the time limits of hazardous cerebral anemia set down by the experimental physiologist.

7. Little or no damage is suffered by the myocardium if the operation of intracardiac injection is performed with the same care and skill exhibited in any other sterile surgical puncture.

8. Many cases have been reported in which resuscitation has been successfully brought about, only to have the patient collapse suddenly and die a few minutes or hours afterward without apparent cause.

9. In properly selected cases, such as those in group 1, a favorable outcome may be expected in about 25 per cent of patients who are apparently dead when treated by the intracardiac injection method.

A NEW CONCEPTION OF RESUSCITATION OF THE STOPPED HEART BY INTRACARDIAC METHODS OF TREATMENT

In considering the large and varied number of substances successfully utilized in intracardiac injection for reanimation of the stopped heart, it appeared to us that the response of the heart was not specific for any one chemical substance. The single constant factor in each injected substance was apparently its irritant action, and this action is effective only as far as the muscle of the heart alone is concerned. When the same drug was injected into the pericardium no effect was noted, while injection into any of the chambers of the heart was only moderately successful.

Closer scrutiny of all of the facts in the problem emphasized the differences seen in the reaction to the injection operation exhibited by the hearts of the two groups discussed before, wherein the normal asystolic heart of group 1 can be more readily stimulated to recontraction than the pathologic heart of group 2.

There is abundant clinical and experimental evidence to show that the asystolic heart of group 1 can be resuscitated by simple mechanical irritation. Condorelli's case [29] is a splendid example of this; each tap on the precordium elicited a pulse beat at the wrist. Korbler's experiments [38] on rabbits showed that while intracardiac injections did little or

38. Korbler, G.: Arch. f. klin. Chir. **150**:115, 1928.

no damage to the myocardium, sometimes a puncture wound alone would reactivate a stopped heart.

With this thought in mind, it occurred to us that the success of the intracardiac injection theory of resuscitation depended more on the puncture of the heart by the injecting needle than on the substance injected.

The truth of this statement is easily verified. If one returns for a moment to a consideration of cardiac physiology, it can be demonstrated that while the heart is made up of specialized mechanisms, each part of the heart retains some vestige of a common embryologic tissue in which the factors of irritability, conductivity, contractility and stimulus production may be latent. In a recent textbook on electrocardiography,[39] we pointed out the teleologic significance of this observation as a potential life-saving mechanism when the orderly sequential phenomena of the cardiac cycle are disturbed.

When such disturbances occur, any myocardial fiber may assume the rôle of the pacemaker of the heart; any point that temporarily becomes more irritable than the sino-auricular node may initiate a stimulus for contraction of the entire heart. This is, in brief, the current theory of the extrasystolic arhythmias of the heart.

When such a point of irritability becomes effective, it occurs before the normal pacemaker has an opportunity to discharge its impulse for the cardiac cycle and a premature beat occurs. If, however, the pacemaker is unable to release its stimulus, some other part of the auricle may become irritable and excite the heart to contract, or the atrioventricular node of Tawara may assume the rôle of the pacemaker.[40]

Thus, nature has attempted to prevent standstill of the heart by providing other mechanisms for stimulating contraction. The myocardium of the normal heart at standstill tends to become very irritable and responsive to any stimulus that is intensive enough to initiate discharge of the electrodynamic factors necessary for contraction of the heart muscle.

This explains the mechanism of resuscitation of the stopped heart by intracardiac injection; the prick of the needle alone may be, and usually is, sufficient to initiate the stimulus required for contraction.

In carefully controlled experiments it can be demonstrated that the first beats of the resuscitated heart are extrasystoles. If the heart has not been too badly damaged by the period of anoxemia through which it has passed during asystole, a normal sinus rhythm may be promptly instituted. On the other hand, when the irritability factors of the

39. Parsonnet, A. E., and Hyman, Albert S.: Applied Electrocardiography, New York, The Macmillan Company, 1929, p. 75.

40. Hyman, Albert S.: Postinfluenzal Bradycardia, Arch. Int. Med. **40**:130 (July) 1927.

myocardium have been grossly disturbed, the puncture wound made by the injecting needle may initiate a series of extrasystoles that occur so rapidly that ventricular fibrillation supervenes with immediate collapse of the heart and death.

This is what probably happens in the cases mentioned in section 8 under the heading "Present Status of Intracardiac Therapy for Resuscitation of the Stopped Heart," in which resuscitation has occurred and the heart has commenced to beat again, only to stop suddenly within a few moments or hours. Liang's [41] patient lived for five hours after intracardiac injection and then "the circulation collapsed"—an apt description.

More accurate observers have suggested that the "second death" has been the result of ventricular fibrillation (Smith [42]). In a case of complete heart block with unconsciousness due to the Stokes-Adams syndrome, Levine and Matton [43] noted a period of ventricular fibrillation following the intracardiac injection of epinephrine; their patient made a favorable recovery, due, perhaps, to the peculiar pathologic changes occurring in auricular and ventricular dissociation.

Opportunity for the clinical demonstration of the mechanical irritation theory of resuscitation of the stopped heart has been afforded in two cases, the first of which is presented here. A boy, aged 12 years, suffered from cardiac collapse while under anesthesia; after all other methods of resuscitation had failed, a long needle was inserted into the left ventricle. The heart contracted promptly, and the patient made an uneventful recovery. No drug was injected, although a syringe containing epinephrine had been prepared for use if the experiment failed. In this case, the mere prick of the needle was apparently enough to start automatic contraction of the heart.

The success of this demonstration led us to a further study of the extrasystolic arhythmias, in an attempt to develop measures for the prevention of ventricular fibrillation and secondary collapse of the heart after resuscitation.

When the ectopic focus of extrasystoles lies in the auricles, the ventricular response is normal in all respects, with the sole exception of its prematurity. The ventricular rate may be very rapid, but the protecting mechanism provided by the junctional tissue and bundle system tends to reduce or filter out many of the stimuli; physiologic block develops and the ventricle beats slower. This is seen clinically in rapid auricular flutter or paroxysmal auricular tachycardia, in which the auricular con-

41. Liang, P. K.: Brit. M. J. **2**:1176 (Dec. 18) 1926.
42. Smith, G. F. R.: Brit. J. Anesth. **4**:207 (April) 1927.
43. Levine, S. A., and Matton, M.: Heart **12**:271 (March) 1926.

tractions may be as high as 300 beats per minute while the ventricular response may run as low as 80.[44]

The sequential development of auricular extrasystoles, auricular flutter and auricular fibrillation is familiar to every cardiologist; such conditions are not incompatible with an active life on the part of the patient.[45] The prognosis of auricular disturbances of the heart is far more favorable than when such conditions affect the ventricles, the difference depending on the hemodynamic factors involved. Whereas irregularities of rhythm and output of the auricles may embarrass filling of the ventricular chambers, the same type of irregularities when occurring in the ventricles disarranges the entire circulation of the body, with immediate hazardous and sometimes fatal results.

A consideration of these facts would tend to indicate, therefore, that the dangers inherent from ventricular fibrillation following the intracardiac injection procedure for resuscitation of the stopped heart might be avoided, if not entirely eliminated, if the puncture was made in the auricles instead of in the ventricles.

A familiar laboratory experiment demonstrates that of the two, the auricles are far more sensitive to mechanical stimulation than the ventricles. In the resuscitation procedure, the auricles should thus be the portion of the heart best adapted physiologically for the reception of the injecting needle. The development of extrasystoles or even fibrillation of the auricles would be relatively unimportant for the reasons previously indicated.

Approach to the right auricle is not difficult. Experiments on cadavers showed that a slightly curved needle could be passed through the third interspace as close to the right sternal margin as possible and penetrate the right auricle. The needle must be directed toward the midline so that the curve carries the point under the sternum; after a little practice, the interns of the hospital found it no more difficult to penetrate the right auricle than to reach the left ventricle at the point generally recommended for intracardiac injection.

In children up to about the age of 12, the right auricle lies within 2 inches (5 cm.) of the anterior surface of the sternum, but in adults this depth may be greatly increased. Average figures obtained in a series of about forty cadavers showed that in thin persons this depth was about 3½ inches (8.87 cm.), while in wide-chested persons the inserted needle must be at least 4½ inches (11.43 cm.) long. In about 60 per cent of the cadavers examined, the injecting needle approached the right auricular appendage first. At this point there is little or no

44. Roth, I. R.: Cardiac Arryhthmias, New York, Paul B. Hoeber, Inc., 1928, p. 169.

45. Hyman, Albert S.: Am. Med. **22**:469 (Aug.) 1927.

danger of penetrating the great vessels, as they lie at least 3 inches (7.6 cm.) above and below this level.

The clinical demonstration of this method of approach to the right auricle was attempted in four cases in which the patients had died as the result of various ailments; the first two had died of pneumonia. Injection into the right auricle was attempted after mere penetration had failed to elicit cardiac activity; no result was obtained. The third case was that of a woman who had died of general carcinomatosis; insertion of the needle into the right auricle in this case was followed by weak, irregular contractions of the heart after there had been complete cardiac standstill for about nine minutes. The heart continued to beat for about seventeen minutes, and then all sounds disappeared.

Results in the fourth case were especially gratifying. The patient, a woman, aged 45, who was suffering from mitral stenosis and with severe decompensation, succumbed to a complete collapse after having had several sinking spells during the previous twenty-four hours. Seven minutes after she had been pronounced dead by the intern on service, a needle was inserted into the right auricle. There was an immediate response on the part of the heart; a very rapid, irregular rate suggesting auricular fibrillation occurred. The needle was quickly withdrawn and in about an hour the patient began to show voluntary movements, although still semiconscious. At this time an intravenous injection of strophanthin and dextrose was given, and after a rather stormy six hour period she became conscious and could speak to those around her. This patient lived for about eight days, finally dying of her cardiovascular disease. No attempt was made to resuscitate her the second time.

To these four cases, which properly belong in group 2 and therefore cannot be considered as suitable for this method of resuscitation, may be added the case of a patient who suffered from cardiac standstill following the manipulation of a fractured femur. The patient was a man, aged 31, who collapsed under anesthesia while the surgeons were attempting reduction. As artificial respiration proved futile, a needle was inserted into the right auricle about six minutes after cardiac arrest. After a very short interval, heart sounds were heard and in about ten minutes the pulse was easily palpable at the wrist and running regular at a rate of 88. The patient made an uneventful recovery.

The total number of resuscitations by the method of stimulating the right auricle by a needle puncture is now about nine cases and includes the unpublished reports of Dr. Joseph B. Wolffe of Philadelphia and Dr. A. E. Parsonnet of Newark, both of whom have undertaken an investigation of this method in their respective cities.

A word in regard to the type of needle used may not be amiss: it has been found that a number 19 gage, all steel needle measuring at least 4½ inches in length is best adapted for intracardiac injections of any

kind. Any gage finer than this becomes too flexible for penetration through the muscles of the chest, while gages larger than 19 become difficult to use. For the resuscitation procedure alone a hollow needle is unnecessary and a solid needle like a long hatpin can be utilized. A hollow needle has generally been used in our cases, since an associated study of intracardiac therapy for certain diseases of the heart has also been carried on by the committee investigating the resuscitation process.

CONCLUSIONS IN REGARD TO THE RESUSCITATION OF THE STOPPED HEART

1. The success of the intracardiac injection procedure for the resuscitation of the stopped heart is apparently due more to the effect of the puncture wound made in the wall of the heart than to the chemical substance injected.

2. The myocardium of the normal asystolic heart rapidly becomes irritable with the onset of anoxemia.

3. Under these conditions, any mechanical stimulation may irritate the heart to automatic contraction, and the success of massage and percussion of the heart for resuscitation can be explained on this basis.

4. The puncture wound made by the injecting needle becomes a focus of increased irritability from which a stimulus for myocardial contraction may be developed.

5. The first contractions of the heart after injection are always extrasystoles.

6. The initial extrasystolic arhythmia may give way quickly to a normal sinus rhythm with prompt recovery on the part of the patient.

7. However, when the period of anoxemia has been so prolonged or so intense that there is considerable disturbance in the electrodynamic factors controlling myocardial contraction, the initial extrasystolic arhythmia may persist and may be quickly followed by a rapid sequence of ectopic beats.

8. Such a condition leads to pathologic fatigue of the ventricles which may be followed by ventricular fibrillation.

9. Ventricular fibrillation is an extremely hazardous disturbance of the heart and is usually accompanied by immediate collapse of the circulation and death of the patient. This phenomenon explains the secondary collapse of the circulation often seen following what has apparently been a successful resuscitation of an asystolic heart.

10. It is suggested, therefore, that the intracardiac puncture be made into the right auricle instead of into the ventricles as is now practiced.

11. Intra-auricular puncture is no more difficult to perform than intraventricular injection; a slightly curved 4 inch needle is inserted into the third interspace at the right sternal margin. The point should be directed downward and toward the midline.

12. The auricles are more responsive to mechanical stimulation than the ventricles; a mere prick of the needle may be sufficient to initiate contraction.

13. Here, as in the ventricles, the first contractions are extrasystolic, the exception being that auricular extrasystoles are followed by normal ventricular contractions; hence the immediate establishment of the normal cardiovascular mechanism of circulation.

14. The sequential development of a rapid auricular extrasystolic arhythmia, auricular flutter and finally fibrillation may not be of special significance so far as the ventricular output to the circulation is concerned, since the phenomenon of physiologic block slows the ventricular rate.

15. Intra-auricular puncture should be attempted in every case of death that occurs as the result of the asystolic heart. The cases most favorable for resuscitation are those not affected by general or cardiovascular disease. In deaths occurring on the operating table, after hemorrhage, shock, anesthesia or other ill defined conditions, like "status lymphaticus," prompt resuscitation may result from this procedure, either alone or combined with other life-saving measures—artificial respiration, transfusion, etc. In asphyxia neonatorum, it may be specific in its prompt initiation of automatic contraction of the heart.

16. Intra-auricular puncture is a procedure that every member of the medical profession should be able to perform quickly and skilfully when emergencies arise in which this life-saving operation may be indicated.

DIABETES MELLITUS

IS CLIMATE A RESPONSIBLE FACTOR IN THE ETIOLOGY?*

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A stay of two years in North China so interested me in the possible relation of climate to the occurrence of certain metabolic diseases (diabetes, pernicious anemia, exophthalmic goiter and Addison's disease) that I decided to make a study of the distribution of these diseases in all countries where deaths from these causes are registered. The annual reports on vital statistics of the various countries supplied the data used. An effort has been made to work out the prevalence of each disease geographically by countries and, where possible, racially. The results are interesting and suggestive from the standpoint of etiology. In order that the bulk of data shall not exceed the limits of space, each disease will be dealt with separately, the subject of this communication being diabetes.

The most reliable statistics indicating the incidence of diseases are those on mortality, and with the "International List of the Causes of Death" in wide use, the rates in various countries may well be compared. The point of greatest variability is, of course, the ability of the physician in naming the cause of death. Undoubtedly, many cases of non-diabetic glycosuria are diagnosed as diabetes, while, on the other hand, numbers of patients have undiagnosed diabetes. Whether these errors counterbalance each other has not been ascertained. The diabetic death rate in cities with large diabetic clinics is not higher than in those without. In the United States the rate is lower in the rural than in the urban districts, while in England and Wales the opposite is the case. It would seem most likely, therefore, that the death rate represents a fairly true picture of the prevalence of the disease. This is all the more true in that all cases in which diabetes is named as a contributory cause of death are classified as cases of diabetes, no matter what the immediate cause of death may have been (except cases of pulmonary tuberculosis, diphtheria and typhoid fever).

It is true, however, that a certain proportion of the apparent increase in the diabetic death rate may be due to improved diagnostic methods. Many patients with mild diabetes discovered more or less by accident in the course of a laboratory examination have the diagnosis of diabetes attached to them for life, and after death, as well. In this way, perhaps

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a considerable part of the apparent increase in the incidence and death rate of diabetes may be only an increase in the recognition of it. This is a statement that does not seem to be susceptible of definite proof.

My observations in China indicate that diabetes among the natives is of low incidence and mild character, and that it is accompanied by definite hypersensitivity to insulin.[1] Reed,[2] in 1915, pointed out the infrequency of the disease among the Chinese. This benign type of diabetes is prevalent among the Japanese, also. Iwai,[3] in a study of hospital cases, saw little diabetic coma. He was particularly impressed by the great difference of the disease there as contrasted with that seen in western countries. Concepcion [4] set forth a similar picture of the mildness of diabetes in the Philippines. It is also said to be infrequent and mild in India, except in the wealthy leisure class, especially that of the Hindus.[5] Mitra [6] called the disease the bane of Bengal, particularly of wealthy and indolent Bengales gentlemen. Christopherson [7] said glycosuria is rare in the Egyptian Sudan. He saw only one case in five years. Martin [8] remarked on the rarity of diabetes among the negroes of the west coast of Africa, but reported three cases as proof that it exists there. Palacios [9] stated that the disease is mild in the coastal area of Venezuela, diabetic coma being practically unknown. The disease is infrequent and the production of acetone bodies slight.

In a symposium on diabetes in the tropics (at meetings of the British Medical Association in 1907),[5] it seemed to be the concensus among physicians who had served in India and the East that in the poorer classes of natives diabetes was infrequent, but that in the wealthy classes and clerical or business classes it was prevalent. This prevalence is often attributed to the unusual nervous strain that these classes undergo in their constant contact with European civilization. The change of diet toward the European type, with more sugar and sweet wines, is often cited as a responsible factor. Cauthie [10] said that Chinese who indulge in European food extensively are prone to have diabetes, while on their native diets they are very free from it. This observation was also made

1. Mills, C. A.: China M. J. **41**:914, 1927.
2. Reed, A. C.: Am. J. M. Sc. **151**:577, 1916.
3. Iwai, T.: Arch. de méd. expér. et d'anat. path. **27**:1, 1916.
4. Concepcion, I.: J. Philippine Islands M. A. **2**:57, 1922-1923.
5. Symposium on Diabetes in the Tropics, British Medical Association Meeting, Exeter, July 27 to Aug. 2, 1907, Brit. M. J. **2**:1051, 1907.
6. Mitra, A.: Indian Lancet, Calcutta **21**:897, 1903.
7. Christopherson, J. B.: Brit. M. J. **2**:1063, 1907.
8. Martin, M.: Arch. f. Schiffs- u. Tropen-Hyg. **10**:363, 1906.
9. Palacios, G. D.: Chimie Pathologique Tropicale de la Région Atlantique, Caracas, Lit. y Tip. del Comercio.
10. Cauthie, James: Brit. M. J. **2**:1063, 1907.

by me in my contact with Chinese students. The ingestion of foreign food for some weeks seemed often to lead to boils and mild glycosuria, which readily disappeared under dietary adjustment. Cauthie likened the intolerance of the tropical or oriental natives for sugar to their well known lack of tolerance for alcohol. He also raised the question whether the prevalence of diabetes among the Jews might not be on some such basis. Morrison [11] found the death rate from diabetes in Boston to be highest in the Irish inhabitants, while table 6, given on a later page, shows the rate in Ireland to be low. Here, again, is a people showing a marked rise in diabetic death rate following their migration from a lower to a higher stage of industrialized civilization.

Gore [12] recently made a study of the world death rate from diabetes and concluded not only that the disease is infrequent in the tropics, but that it is showing the most alarming increase in rate in the United States, Canada, northern Europe, Australia and New Zealand. Williamson [13] and Hoffman [14] set forth similar data.

When one contrasts the diabetes in the Orient and Tropics, as described in the reports named, with the disease as it is known in the northern part of the United States, in Canada and north central Europe, one is led to wonder whether important factors other than race and diet may not be working to determine its etiology. It was in an effort to evaluate the climatic factor more closely that the present work was undertaken. Individual countries were studied by states or provinces, when possible; continents were studied as to the prevalence in the constituent countries, and finally the world distribution by countries was studied as completely as possible.

DIABETES IN VARIOUS COUNTRIES

United States.—Because of the climatic extremes to be found in the United States, both as to temperature and as to humidity, the study was begun with this country. The report of the Bureau of the Census "Mortality Statistics: 1926" in the registration area for 1920, 1925 and 1926 was used. In table 1 are given the rates for the states of the registration area. The rate given in each case represents the mean of the crude rates for 1920, 1925 and 1926, so that annual irregularities may be minimized. It is seen that the states may readily be arranged in geographic groups according to the diabetic death rate, the southern states being lowest, the western plateau and mountain states coming next,

11. Morrison, H.: Boston M. & S. J. **174**:54, 1916.
12. Gore, J. K.: A World's War on Diabetes, Newark, N. J., Prudential Insurance Company of America, 1927.
13. Williamson, R. T.: Med. Chron., Manchester **50**:234, 1909.
14. Hoffman, F. L.: Boston M. & S. J. **187**:135, 1922.

then the northern states from Michigan west, the middle states from the Atlantic ocean to the Pacific ocean and finally the northeastern states, with a rate 2.2 times as high as that of the southern group (table 1).

A grouping of the cities of over 100,000 population into three belts across the country from west to east shows equally striking differences in the diabetic death rate (table 2). Thus the rate rises from 14.1 per hundred thousand estimated population in the southern cities to 20.4 in the central area, and 23 in the north. And if one omits the four cities, Detroit, Toledo, Cleveland and Youngstown, from the northern group,

TABLE 1.—*Deaths from Diabetes Mellitus per Hundred Thousand Estimated Population in the States of the Registration Area of 1926* *

Florida	11.8	California	18.6
South Carolina	7.6	Kansas	17.4
Alabama	7.6	Nebraska	19.3
Mississippi	8.1	Iowa	19.3
Louisiana	9.6	Missouri	15.3
Arizona	8.3	Illinois	19.8
Tennessee	7.6	Indiana	17.9
North Carolina	8.3	Ohio	18.0
Virginia	11.0	Pennsylvania	18.0
West Virginia	9.8	Delaware	16.4
Kentucky	9.3	Maryland	19.3
		New Jersey	20.3
Mean for 11 states	9.9		
		Mean for 12 states	18.3
Colorado	12.7		
Utah	12.1	Maine	22.5
Wyoming	9.9	Vermont	21.0
Montana	10.4	New Hampshire	23.4
Idaho	8.3	Massachusetts	20.2
		Connecticut	21.2
Mean for 5 states	11.1	Rhode Island	21.8
		New York	24.4
Washington	15.6		
Oregon	18.1	Mean for 7 states	22.1
North Dakota	15.6		
Minnesota	17.1		
Wisconsin	18.0		
Michigan	17.0		
Mean for 6 states	16.9		

* Figure given for each state is the mean of the rates for 1920, 1925 and 1926.

its rate rises to 24.3, which is more than 1.7 times the rate of the ten southern cities. The four cities named, with a mean rate of 15.9, fall so definitely out of line with other northern cities around them that an explanation was sought for in the statistics of population. The probable reason was readily found. During the last twenty years, these four cities, in particular, have shown a phenomenal increase in population, and a large percentage of this increase has come from the countries of southern Europe, including Russia. This inclusion of a large percentage of southern European nationalities serves as a likely cause of the low diabetes death rate in these cities, bringing it closer to that of the southern cities. Pittsburgh was affected to a slightly less degree. For instance, the percentage of foreign-born parents of children born in 1918 was 48 per cent for Cleveland, 44 per cent for Youngstown, 35 per cent for

Detroit and Pittsburgh and 21 per cent for Toledo. Only four other cities had 35 per cent, or more, of foreign-born parentage in that year, these being New York, Providence, Scranton and Buffalo. No reason can be found to explain why Buffalo should differ so markedly in its diabetic death rate from the other cities on Lake Erie.

Among the southern states, Florida ranks highest, just as does Colorado among the mountain and plateau states. One would be inclined to attribute this largely to migration from the north of wealthy

TABLE 2.—*Deaths from Diabetes Mellitus per Hundred Thousand Estimated Population in the Cities of the Registration Area of 1926* *

San Antonio	11.9	Spokane	20.8
Fort Worth	9.3	St. Paul	24.3
Dallas	14.2	Minneapolis	21.4
Memphis	16.0	Milwaukee	21.6
New Orleans	19.6	Chicago	22.5
Nashville	15.6	Grand Rapids	23.9
Atlanta	13.3	Detroit	15.0
Birmingham	13.1	Toledo	16.7
Richmond	16.6	Cleveland	16.8
Norfolk	11.9	Youngstown	15.1
Mean for 10 cities	14.1	Buffalo	26.0
		Rochester, N. Y.	23.6
San Francisco	21.7	Scranton	24.9
Oakland	21.2	Albany	32.7
Salt Lake City	18.1	New York	25.7
Denver	16.7	Newark	23.1
Kansas City, Kan.	20.2	Paterson	25.8
Kansas City, Mo.	15.6	Yonkers	26.4
Omaha	22.0	Syracuse	27.7
Des Moines	17.4	Jersey City	20.0
St. Louis	20.1	New Haven	29.4
Indianapolis	21.1	Springfield, Mass.	22.7
Louisville	19.5	Providence	34.7
Cincinnati	26.8	Fall River	20.8
Dayton	22.0	Boston	23.6
Columbus	21.3	Mean for 25 cities	23.0
Pittsburgh	19.1	Mean for Detroit, Toledo, Cleveland and Youngstown	15.9
Philadelphia	21.2		
Baltimore	24.2	Mean for 21 other cities	24.3
Washington	19.7	Two cities showing greatest increase in 1926 were Albany (102%) and Spokane (93%)	
Wilmington	18.0		
Mean for 19 cities	20.4		

* Figure given for each city is the mean of the rates for 1920, 1925 and 1926.

people, among whom diabetes is more common. The same discrepancy is seen in the death rate from pernicious anemia in these two states (as will be shown in a subsequent paper).

Thinking that perhaps a low total death rate in the western states might account for the low diabetic rate, I prepared a table showing the percentage of the total deaths that were classified as resulting from diabetes. Table 3 presents this data for the forty-one states of the registration area, the mean of the rates for 1920, 1925 and 1926 being used, except as indicated. When viewed in this light, the southern states stand alone, with percentages well below 1 per cent, the mountain and plateau states coming next with figures slightly above 1 per cent, while the percentages of the rest of the northern states range up to more than 2 per cent.

In any discussion as to why the South should have less diabetes than the North, one always encounters the question of the prevalence of the disease among the negroes. One usually hears the terms "uncommon" or "infrequent" with reference to the incidence of this disease among

TABLE 3.—*Diabetic Death Rate in Relation to Total Death Rate*

	Mean Crude Death Rate for 1920-1925-1926 per 1,000 Population	Mean Crude Diabetic Death Rate for 1920-1925-1926 per 100,000 Population	Diabetic Death Rate as Percentage of Total Death Rate
Southern States			
Florida	13.8	11.8	0.85
South Carolina	13.0	7.6	0.58
Alabama	11.8 (1925-1926)	7.6	0.64
Mississippi	12.7	8.1	0.64
Louisiana	12.6	9.6	0.76
Arizona	12.5 (1926)	8.3	0.66
Tennessee	12.1	7.6	0.63
North Carolina	12.1	8.3	0.69
Virginia	12.4	11.0	0.81
West Virginia	10.7 (1925-1926)	9.8	0.92
Kentucky	11.7	9.3	0.80
Rocky Mountain States			
Colorado	12.7	12.7	1.00
Utah	10.1	12.1	1.21
Wyoming	8.2 (1925-1926)	9.9	1.21
Montana	9.0	10.4	1.13
Idaho	7.0 (1925-1926)	8.3	1.19
Washington	10.5	15.6	1.49
Oregon	11.4	18.1	1.59
North Dakota	8.4	15.6	1.93
Minnesota	10.0	17.1	1.71
Wisconsin	10.7	18.0	1.68
Michigan	12.6	17.0	1.35
California	13.6	18.6	1.37
Kansas	10.7	17.4	1.63
Nebraska	9.4	19.3	2.05
Iowa	10.2	19.3	1.90
Missouri	12.2	15.3	1.25
Illinois	12.0	19.8	1.65
Indiana	12.9	17.9	1.39
Ohio	12.0	18.0	1.50
Pennsylvania	12.8	18.0	1.41
Delaware	14.0	16.4	1.17
Maryland	14.3	19.3	1.35
New Jersey	12.3	20.3	1.65
Maine	14.5	22.5	1.55
Vermont	14.9	21.0	1.41
New Hampshire	14.3	23.4	1.59
Massachusetts	12.9	20.2	1.57
Connecticut	12.1	21.2	1.75
Rhode Island	13.0	21.8	1.68
New York	13.3	24.4	1.84
Registration states	12.3	17.1	1.39

them, and the question arises whether this might not account for the low diabetic rate in the southern states. However, Lehman [15] found that in the hospital it is as prevalent among negroes as among white people. In table 4 is given the mean of the rates for 1920, 1925 and 1926 for each

15. Lehman, I. I.: New Orleans M. & S. J. **63**:461, 1910-1911; Southern M. J. **14**:522, 1921.

of the states in which deaths are classified by race. The term "colored" includes all races other than the white, but refers so preponderantly to the negro that other races in the South can be disregarded. In table 4, it is seen that there are almost as many deaths from diabetes among the "colored" as among the "white" population, in two states the number of deaths among the "colored" even being the greater. It is also important to notice that the three states having the highest diabetic death rate among colored persons are the states located farthest north in the group given. A geographic grouping of the cities, in which classification is by race, again

TABLE 4.—*Deaths from Diabetes Mellitus per Hundred Thousand Estimated Population in the States and Cities of the Registration Area in Which Classification into "White" and "Colored" Is Made*

States	Death Rate per 100,000	
	White	Colored
Alabama	7.8	7.0
South Carolina	9.2	6.1
North Carolina	8.7	7.4
Tennessee	7.4	8.4
Mississippi	10.1	6.3
Louisiana	10.7	7.8
Florida	14.3	6.6
Kentucky	9.0	12.4
Virginia	11.3	10.2
Maryland	20.6	13.1
Mean rate	9.8	8.5

Cities	Death Rate per 100,000	
	White	Colored
Fort Worth	9.5	7.9
Dallas	14.2	15.3
Birmingham	15.2	9.8
Atlanta	13.1	14.2
New Orleans	19.5	19.9
Memphis	16.5	15.3
Nashville	15.3	16.0
Norfolk	13.0	9.5
Richmond	18.2	12.8
Mean rate	14.9	13.4
Washington	18.7	22.9
Baltimore	25.4	17.3
Louisville	20.0	16.8
Indianapolis	21.8	15.6
Kansas City, Mo.	19.9	22.3
Mean rate	21.2	19.0
Mean rate for all the above cities	17.1	15.4

emphasizes the points just mentioned: that diabetes is almost as prevalent in the negro as in the white race, and that the rate increases with about equal rapidity in both races as one goes from south to north. In two states and six large cities, the rate for the colored is higher than that for the white population.

In view of these observations, it may well be concluded that the negro is not responsible for the low diabetic death rate in the southern states. The statistics for the negro race greatly strengthen the evidence pointing toward a climatic effect in the etiology of diabetes. In two districts of Nigeria, where registration of death by cause is compulsory, the diabetic death rate among the natives in 1926 and 1927 was less than one per hundred thousand of population. The farther the negro gets from his natural tropical environment, the higher the number of deaths from diabetes. It would be extremely interesting to have a similar study of the Jews to see whether the high incidence of diabetes among them lessens with a lessening of the distance from the equator.

In order to be sure that age and sex differences in the population of the various states are not the factor responsible for the differences seen in the incidence of diabetes, the states were arranged in the same groups as before, and the adjusted diabetic death rate was studied for the year 1921.[16] The mean rate for the southern states rose from 9.2 to 9.8, that for the western mountain states from 12.8 to 14.3, while the rate for the northern states fell, the fall being greatest in the New England states that had the highest rate. The rate here fell from 23.6 to 19.7. Thus, although the use of adjusted rates tends to lessen the divergence north and south, the same geographic differences are maintained, the mean southern rate being less than half the northeastern rate.

A similar comparison of the crude and the adjusted diabetic rates for 1921 in the eleven states in which the classification is by color shows the adjusted rate for white people to be 12.6 and the crude rate 12.4, while

TABLE 5.—*Death Rate from Diabetes in Canada*

	Total Number of Deaths per 1,000 Population	Deaths from Diabetes per 100,000 Population	Deaths from Diabetes as Percentage of Total Number of Deaths
Prince Edward Island	12.0	10.6	0.88
Nova Scotia	12.2	11.1	0.91
New Brunswick	12.8	11.1	0.87
Quebec	14.5 (1926)	11.0	0.76
Ontario	11.35	11.9	1.05
Manitoba	8.55	8.2	0.96
Saskatchewan	7.45	6.2	0.83
Alberta	8.35	8.0	0.96
British Columbia	8.95	11.0	1.23

* Mean rates for the years from 1921 to 1926, inclusive.

the adjusted rate for colored people is 9.9 as compared with a crude rate of 8.4. The adjusted rate for the colored race shows the same marked increase as one goes northward as was seen in table 4. New York and Pennsylvania, not given in table 4, have an adjusted rate for the colored population much higher than that in the south. In Pennsylvania, the rate is 5 higher than that for the white race.

Canada.—The diabetic death rate of Canada as a whole is considerably below that of the United States, but shows the same variations from east to west as does the northern half of the latter country. Table 5 shows the mean crude rate per hundred thousand of population for the years 1921 and 1926 in the various provinces and the deaths from diabetes as percentages of the total number of deaths.

One sees here that the greatest incidence of diabetes in Canada is in those provinces nearest to the New England states, where the death rate from diabetes in the United States is highest. Also, the prairie provinces

16. Gover, Mary: Pub. Health Bull., no. 174, U. S. P. H. S., Washington, 1928.

have a low rate corresponding to that of the western plateau and mountain states in this country. The same elevation is again noted for the Pacific coast. However, when one considers only the proportion of the total number of deaths due to this cause, there are no striking differences in the different provinces.

The Registration Countries of Europe.—The death rate from diabetes was available for fourteen countries of Europe, as given in table 6. When one groups the countries into those with a rate above 9.6 and those with one of 9.6 or below, as is done in table 6, a striking geographic separation is seen. With the exception of Ireland, all the countries above the fiftieth parallel the death rate of which is available, have a death rate from diabetes above 9.6, while all below that parallel have a rate of 9.6 or below. Thus, with the exception of Ireland, the fiftieth

TABLE 6.—*Diabetic Death Rate in the Countries of Europe*

Countries	Year	Diabetic Death Rate per 100,000 of Population	Deaths from Diabetes as Percentage of Total Number of Deaths
Netherlands	1927	16.3	1.59
Denmark	1927	12.9	1.12
England and Wales	1927	12.6	1.02
Belgium	1927	13.3	0.99
Sweden	1925	11.3	0.96
Norway	1926	9.7	0.90
Scotland	1927	10.6	0.79
North Ireland	1927	9.6	0.66
Switzerland	1925	9.2	0.75
Spain	1926	8.5	0.45
Irish Free State	1927	7.8	0.53
Italy	1925	5.9	0.35
Czechoslovakia	1926	5.4	0.36
Hungary	1927	4.3	0.24

parallel forms a sharp division in the incidence of diabetes in Europe. This difference north and south is even more striking when one considers the deaths from diabetes in relation to the total deaths, as is done in the second column of table 6. A further point of great importance is that the rate is at present increasing much more rapidly in the northern European countries than in the southern. No doubt Germany would fall in the northern group if the country's rate were available. Morrison [11] found that the German inhabitants in Boston had a comparatively high rate.

Australia, Tasmania and New Zealand.—In Australia, Tasmania and New Zealand, one has, again, a large area showing a distribution of diabetes north and south, just the reverse of that of Europe and the United States. Table 7 shows this increase toward the south and away from the equator.

Africa, Asia and South America.—The only data available for Africa on deaths from diabetes per hundred thousand of population

were: Nigeria, 1; southern Rhodesia (European population), 8, and Union of South Africa, 11.6. Even this limited number arrange themselves with an increasing rate as the distance from the equator increases.

In Asia, the rate for a whole population was given only in three countries: Japan, 3.19; Straits Settlement, 2.7, and Ceylon, 6.5. A few city rates are given, and many for hospitalized population, but these are of little value in such a study as this.

It is of particular interest to note that Japan, lying as far north as it does, has a tropical rate. The same is true of the whole of China, although no reliable statistics are available. What relation this low rate bears to the severe tropical summer that prevails along the entire coast of Asia is questionable. The coincidence, however, is suggestive.

On the basis of latitude, one would expect China to show the same difference in incidence of diabetes north and south as is encountered in

TABLE 7.—*Mean Diabetic Death Rate per Hundred Thousand Population in Australia, Tasmania, and New Zealand for the Years from 1921 to 1927 Inclusive*

1. Western Australia	10.2
2. Northern Territory	0.0
3. Queensland	9.3
4. South Australia	15.3
5. New South Wales	11.7
6. Victoria	12.1
7. Tasmania	13.5
8. New Zealand	11.9

the United States. The winters in North China are severe, as contrasted with those in South China, but the summers are about equally depressing throughout. In South America, the rate is everywhere low. Time relationships in the data of these countries are not sufficiently uniform to warrant a close comparison.

Throughout the Registration Areas of the World.—In table 8 are presented the death rates from diabetes by countries for all areas giving such data. It is seen here that certain areas of the earth supply all the high rates, these being northwestern Europe (including the British Isles), the United States and Canada in North America, southern Africa, and Australia, Tasmania and New Zealand. These countries are the ones principally dominated by the people from northern Europe, but one cannot safely assume that this accounts for the high incidence of diabetes. For instance, Anglo-Saxons of the United States have a high rate in the North and a low one in the South. Rather, it seems better to assume that the same advantageous factors that led to the development in these regions by northern Europeans, may also be causing the increase in diabetes. The climatic stimulation, in increasing the vigor and ambition of the people so as to lead to great developments along all lines of

endeavor, may also be causing the body to exceed its metabolic capacity in various ways. This overwork, or exhaustion, may show itself in diabetes mellitus, suprarenal insufficiency of the degree seen in the so-called "neurocirculatory asthenia" and particularly in nervous and mental diseases of the exhaustive type. Unfortunately, accurate statistics

TABLE 8.—*Death Rate from Diabetes Mellitus in the Registration Countries of the World*

Country	Year	Crude Diabetic Death Rate per 100,000 of Population	Deaths from Diabetes as Percentage of Total Number of Deaths
United States	1926	18.0	1.47
Netherlands	1927	16.3	1.50
New Zealand	1927	13.7	1.02
Belgium	1927	13.3	0.99
Denmark	1927	12.9	1.12
Australia	1927	12.9	1.37
England and Wales	1927	12.6	1.02
South Africa	1926	11.8	1.23
Canada	1927	11.4	1.14
Sweden	1925	11.3	0.86
Scotland	1927	10.6	0.79
Norway	1926	9.7	0.80
North Ireland	1927	9.6	0.66
Switzerland	1925	9.2	0.75
Spain	1926	8.5	0.45
Hawaii	1927	8.5	0.75
Southern Rhodesia (Europeans only)	1925	8.0	....
Saar Basin	1927	8.0	....
Irish Free State	1927	7.8	0.53
Barbados	1927	7.1	0.35
Province of Buenos Aires	1924	6.7	0.60
Ceylon	1928	6.4	0.26
Italy	1925	5.9	0.35
Uruguay	1927	5.5	0.48
Czechoslovakia	1926	5.4	0.36
Curaçao	1927	4.7	....
Hungary	1927	4.3	0.24
Jamaica	1927	4.2	0.19
Grenada	1927	4.1	0.26
Cuba	1925	4.1	0.32
Paraguay	1928	3.7	0.25
British Guiana	1928	3.7	0.13
Colombia	1927	3.5	0.24
Argentina	1913	3.5	0.22
Chile	1927	3.5	0.14
Japan	1924	3.2	0.15
Costa Rica	1927	3.1	0.21
Straits Settlement	1927	2.8	0.09
Venezuela	1918	2.5	0.13
Iceland	1911–1915	2.0	0.14
Province of Mendoza	1924	2.0	0.11
Province of Tucumun (Argentina)	1928	1.5	0.08
Panama	1926	1.1	0.09
Nigeria	1926	1.0	0.04
Philippine Islands	1925	0.5	0.03
Haiti	1927	0.4	0.08

can be had only for diabetes. In a subsequent paper, it will be shown that pernicious anemia has a distribution similar to that of diabetes, indicating the possibility of its also having a climatic relationship.

A strong argument against the claim that the racial factor is the most important in the distribution of diabetes is the marked change in the death rate from diabetes of the negroes in this country as one goes from south to north, a change even more marked than that of the corresponding rate for the white race. It would seem much more likely that either

the more intense type of living necessary in the highly industrialized areas causes the increase or the same climatic factors that cause the development of the area likewise increase the disease. There is a strong correlation between Huntington's "energy maps" of the world [17] and the rate maps for diabetes which one may construct from the data given here. Where he found the climatic stimulation most evident in the energy of the people, there also one finds the highest incidence of diabetes. This holds for the different parts of the United States, as well as for the whole world. It fails to hold, however, for Japan.

COMMENT AND SUMMARY

The significance of the salient points in the data has been discussed as the figures were presented in each section. It may be well, however, to emphasize still further certain features of the presentation.

That the incidence of diabetes in the southern states is definitely and markedly lower than in the northern states of this country is beyond doubt. This difference is about equally great for both white and colored races as one goes from south to north. Nor can the low southern rate be attributed to the large negro population, for the death rate of the latter from diabetes is only slightly below that of the white population in any given state. In fact, in a few states and cities it is higher.

This same climatic distribution of the disease is seen also in Australia, Tasmania and New Zealand, where the rate increases as the distance from the equator becomes greater. This occurs with practically a homogeneous population. In Europe, one finds a division along the fiftieth parallel, with a high rate north and a low rate south. That this division should be found in Europe, with its great diversity of people, and with no outstanding dietary factors to which it might be attributed, forms a rather strong indication of climatic effect.

Japan and north China, with the scarcity and mildness of the diabetes of these countries, supply an apparent exception to the climatic distribution, but here one may readily attribute the low rate to the long moist tropical summer which along the Asiatic coast extends almost to the Arctic circle.

Many writers have suggested that increased consumption of sugar may be the major factor responsible for the increase in diabetes. It seems undoubtedly true that certain races do exhibit a proneness to diabetes when they leave their native diets for the foreign foods containing more sugar (Chinese, especially). It may also be true that the people of the northern section of the United States consume more sugar

17. Huntington, Ellsworth: World Power and Evolution, New Haven, Conn., Yale University Press, 1920, p. 230.

than do those in the south, although no proof either for or against this is at hand. But in Europe one can scarcely accept dietary differences as responsible factors in determining the incidence of diabetes north and south. Nor would there exist such a difference in diagnostic ability in the medical profession in northern and southern Europe.

Racial traits have also been credited with determining the incidence. But here one can cite the low rate for the Irish in Ireland and the high rate for this nationality in this country (Boston), also the difference in the Chinese when they live on their native diets and when they eat foreign foods. The negroes, again, contradict the assumption of a racial element, with their extremely low rate in Africa, moderately low rate in the southern states and high rate in the northern states of this country.

One can therefore scarcely avoid the conclusion that climate is a factor that is, in part at least, responsible for the incidence of diabetes in all races. The regions possessing the most changeable and stimulating climate are the ones with the highest incidence of diabetes. In some of these, it is true, life is intense and complex, and the sugar consumption high, indeed, but in certain others, equally stimulating, almost the same frequency of diabetes is seen without the high sugar consumption to which to attribute it. One is inclined to attribute the increase in diabetes and consumption of sugar to the same cause, namely, overstimulation by a highly changeable climate, leading to a desire for the sugars as readily available producers of energy, but also leading to an increase in diabetes whether this desire for sweets is satisfied or not. The increase is probably much more marked where the prosperity of the people permits them to indulge this desire without stint. Prosperity may also act by lessening the physical effort required, thus making the intake of sugar still more excessive so far as physiologic needs are concerned.

DIABETES MELLITUS

SUGAR CONSUMPTION IN ITS ETIOLOGY *

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In the preceding paper on the relation of climate to the death rate from diabetes,[1] a definite climatic distribution of the disease was pointed out. In the United States, for instance, the death rate from diabetes was over twice as high in the northern as in the southern states, and this difference was even more marked in the colored than in the white population. Europe showed a similar increase in the death rate from diabetes toward the north, as did the provinces of Australia and New Zealand in the opposite direction. This definite tendency in the distribution of the disease raises the question of whether climate is the responsible factor, or whether a higher rate of consumption of sugar in the northern states and countries might not cause the increase. It has often been suggested that overindulgence in sugar may bring on diabetes, a suggestion that seems to be borne out frequently by case histories. However, no definite proof has yet been offered. Emerson and Larimore [2] were of the opinion that a rather close relationship existed between annual consumption of sugar and the death rate from diabetes in the United States, Great Britain and Paris. If a cause and effect relationship were to exist, one would expect a lag of several years in the rise of diabetes rather than a parellelism with the consumption of sugar, since only the initiation of the disease would thus be influenced and not its course or duration under treatment.

In the accompanying table is given the consumption of sugar in kilograms per capita for five years (1923-1928), together with the death rate from diabetes for the most recent year obtainable, and the deaths expressed from diabetes as a percentage of the total deaths. A study of this table fails to show any direct relationship between consumption of sugar and deaths from diabetes. Some countries with a high consumption of sugar, as Hawaii, Argentina and Cuba, have a relatively low death rate from diabetes, while some of the countries with a high death rate from diabetes, such as the Netherlands and the Union of

* Submitted for publication, March 3, 1930.

* From the Department of Internal Medicine, University of Cincinnati.

1. Mills, C. A.: Diabetes Mellitus: Is Climate an Important Etiologic Factor? Arch. Int. Med., this issue (**46**:569, 1930).

2. Emerson, Haven; and Larimore, Louise S.: Diabetes Mellitus, Arch. Int. Med. **34**:585 (Nov.) 1924.

Table Showing Consumption of Sugar and Death Rate from Diabetes

Table Showing Consumption of Sugar and Death Rate from Diabetes

Country	Consumption of Sugar, Kilograms per Capita				
	1923-1924	1924-1925	1925-1926	1926-1927	1927-1928
Australia	59.9	58.7	58.3	58.2	58.0
Hawaii	54.4	54.7	55.0	55.0	55.1
Denmark	48.2	49.7	53.8	48.6	51.7
United States	49.2	52.5	52.2	51.3	49.6
Argentina	27.8	30.0	32.7	31.9	31.1
Cuba			46.6*		
Great Britain	33.1	35.6	44.0	44.9	44.3
Switzerland	38.4	40.6	41.2	41.1	44.8
Canada	36.8	36.3	39.7	34.3	42.5
Sweden	40.0	41.9	41.4	40.3	40.8
New Zealand	33.8	37.1	37.0	35.9	37.7
Norway	46.0	50.0	37.7	34.1	29.5
Netherlands	23.0	28.0	27.0	30.4	31.4
Austria	26.8	28.6	28.7	26.3	30.0
Czechoslovakia	22.9	26.7	29.8	26.3	30.0
Belgium	25.8	27.6	28.6	25.7	27.0
Germany	21.9	24.9	24.6	24.4	26.4
France	14.6	22.2	22.6	23.9	25.4
British Guiana	20.6	23.1	24.2	20.1	23.8
South Africa	....	21.4*	....	....	....
Uruguay	17.0	17.5	19.1	20.0	20.3
Chile	....	....	....	22.3*	21.4*
Central America	25.0*	20.2*	....	....	....
Hungary	13.1	12.4	12.4	14.5	14.5
Mexico	6.0	10.2	11.0	12.4	13.5
Poland	10.1	10.6	11.6	13.3	13.3
Japan and Formosa	7.2	9.8	10.1	11.5	12.7
Japan	8.4	8.6	9.3	9.2	10.3
Portugal	....	....	12.4*	12.7*	....
Spain	....	....	12.7*	12.7*	....
Jamaica	10.5	10.8	10.8	11.9	12.2
Philippine Islands	....	....	....	11.5*	....
Italy	....	....	....	9.5*	....
Russia	8.7	8.4	8.9	8.9	9.1
Haiti and Santo Domingo	3.2	5.3	7.1	7.4	8.9
China	3.8	3.9	3.8	4.3	4.2
	2.1	2.4	2.3	2.0	2.2

Country	Year	Crude Estimate of Death Rate from Diabetes per 100,000 Population	Deaths from Diabetes as Percentage of Total Deaths
New Zealand	1927	13.7	1.02
Netherlands	1927	16.3	1.59
United States	1926	18.0	1.47
Australia	1927	12.9	1.37
South Africa	1926	11.8	1.23
Canada	1927	11.4	1.14
Denmark	1927	12.9	1.12
England and Wales	1927	12.6	1.02
Belgium	1927	13.3	0.99
Sweden	1925	11.3	0.96
Norway	1926	9.7	0.90
Scotland	1927	10.6	0.79
Switzerland	1925	9.2	0.75
Hawaii	1927	8.5	0.75
North Ireland	1927	9.6	0.66
Province of Buenos Aires	1924	6.7	0.60
Irish Free State	1927	7.8	0.53
Uruguay	1927	5.5	0.48
Spain	1926	8.5	0.45
Czechoslovakia	1926	5.4	0.36
Barbados	1927	7.1	0.35
Italy	1925	5.9	0.35
Cuba	1925	4.1	0.32
Grenada	1927	4.1	0.25
Paraguay	1928	3.7	0.25
Hungary	1927	4.3	0.24
Colombia	1927	3.5	0.24
Argentina	1913	3.5	0.22
Costa Rica	1927	3.1	0.21
Jamaica	1927	4.1	0.19
Japan	1924	3.2	0.15
Chile	1927	3.5	0.14
British Guiana	1928	3.7	0.13
Province of Mendoza (Argentina)	1924	2.0	0.11
Province of Tecuman	1928	1.5	0.08
Panama	1926	1.1	0.09
Haiti	1927	0.4	0.08
Philippine Islands	1925	0.5	0.03

* The figures for consumption of sugar were taken mainly from a bulletin on sugar issued by the League of Nations ("The World Sugar Situation," Report by the Economics Committee of the League of Nations, Geneva, July 4, 1929.) They were checked, in most instances, against consumption as obtained from the annual statistical reports of the various countries. When considerable discrepancy was found or when no data were given in the bulletin, the figures obtained directly from the original annual reports are given.

South Africa, come fairly well down in the column of sugar consumption. It is to be noted, however, that of the thirteen countries highest in consumption of sugar, eleven are found among the thirteen highest in death rate from diabetes (including England and Wales, Scotland and North Ireland under the heading of Great Britain).

In like manner, when one considers particular countries, there is again found no constant relationship between the consumption of sugar and the death rate from diabetes. In some that have shown a gradual but steady increase in the consumption of sugar for many years, there has occurred a recent decline in deaths from diabetes. Norway is an instance of this fact, with a consumption of sugar rising gradually from 4.5 Kg. per capita in 1866-1870 to 30.4 Kg. in 1927 and to 31.4 in 1928, while the death rate from diabetes has declined from 11.9 in 1922 to 9.7 in 1926. In Australia, with a high consumption of sugar, the number of deaths from diabetes showed little or no tendency to increase from 1921 to 1926. New Zealand, with a rather marked decline in the consumption of sugar (46.0 Kg. in 1923, 50.0 in 1924, 37.7 in 1925, 34.1 in 1926, and 29.5 in 1927) continues with practically no change in the death rate from diabetes. Hawaii, with a high consumption of sugar for several years, is exhibiting a considerable increase in diabetes. In the United States, the consumption of sugar has been fairly constant for several years, but diabetes continues its alarming increase.

I might cite various other instances to illustrate the lack of any uniformity between the intake of sugar and the deaths from diabetes, but the variability is so great that no further details seem necessary. Lack of space prevents the presentation of all the data on which these statements are made, but the study of the entire mass of data leaves little doubt in my mind that consumption of sugar as such is not related in a causal way to the death rate from diabetes.

BLOOD PLATELETS

AN IMPROVED INDIRECT METHOD FOR THEIR ENUMERATION *

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Numerous methods for counting blood platelets have appeared since Schultze's [1] original description in 1865 of these "granular formations" as microscopic cellular constituents of normal blood. Hittmair [2] in his recent review of the literature referred to twenty new methods that had appeared within the previous ten years. That these methods are for the most part unsatisfactory is indicated by the wide range of supposedly normal figures reported, as shown in table 1.

These wide differences may be explained by improper technic, which involves two kinds of errors: (1) loss or destruction of blood platelets and (2) the inclusion in preparations of artefacts and foreign matter which are mistaken for platelets. The first results in counts too low, the second in counts too high. The difficulties encountered by various investigators are undoubtedly due to the peculiar physical characteristics of the platelets; viz., their great tendency to agglutination, adhesion and easy disintegration, which may occur as soon as they come under conditions that differ from those existing within normal blood vessels. To these must be added their small size and light weight.

Boshamer [3] in his recent investigations found that the blood platelets may be classified into four types: (1) small or young forms, about one-fourth the diameter of a red cell; (2) round to rod-shaped forms, from about one-fourth to two-thirds the diameter of a red cell; (3) rod-shaped forms, and (4) large or giant forms, over two-thirds the diameter of a red cell. Type 1, according to Boshamer, is the most abundant, but also the least resistant, and under unfavorable conditions is apt to undergo rapid disintegration, reducing at times the normal platelet count to one-half its true value.

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* Submitted for publication, Feb. 18, 1930.

* From the Medical Clinic of the Boston Dispensary, Service of Dr. Joseph H. Pratt, and the Division of Research.

1. Schultze, M.: Ein heizbarer Objecttisch und seine Verwendung bei Untersuchungen des Blutes, Arch. f. mikr. Anat. **1**:1, 1865.

2. Hittmair, A.: Die Blutplättchen (review of the literature for ten years), Folia haemat. **35**:156, 1928.

3. Boshamer, K.: Ueber Zählung, Resistanz, und Neubildung von Blutplättchen, Ztschr. f. d. ges. exper. Med. **48**:631, 1925-1926.

If a correct count of the platelets in the circulating blood is to be obtained and a satisfactory normal standard reached, all these facts must be taken into consideration.

The essentials of a good method for counting blood platelets are:

1. A satisfactory preserving fluid.

2. Absence of contact between the undiluted blood and any surface to which the platelets tend to adhere.

3. A technic for the enumeration of the platelets which obviates the necessity of the graduated pipet and of the counting chamber.

THE PRESERVING FLUID

The lack of a satisfactory preserving fluid is the source of error in many of the methods. It is not easy to find a fluid in which the platelets do not stick to one another, to the erythrocytes or to the

TABLE 1.—*Average Number of Blood Platelets per Cubic Millimeter of Normal Blood as Determined by Various Methods*

Average Number of Platelets per C.Mm.	Author
150,000-200,000	Sahli, H.: Ztschr. f. klin. Med. **56**: 264, 1905
228,000	Helber, E.: Deutsches Arch. f. klin. Med. **81**: 316 (Sept.) 1904
234,000	Fonio, A.: Deutsche Ztschr. f. Chir. **117**: 176 (June) 1912
250,000	Bizzozero, J.: Virchows Arch. f. path. Anat. **90**: 261, 1882
297,000	Wright, J. H., and Kinnicutt, R.: J. A. M. A. **56**: 1457 (May 20) 1911
300,000	Kristenson, A.: Acta med. Scandinav. **57**: 301, 1922
366,000	Gram, H. C.: Acta med. Scandinav. **54**: 1, 1920-1921
469,000	Pratt, J. H.: J. A. M. A. **45**: 1989 (Dec. 30) 1905
500,000	Prus, J.: Medycyna, 1886, nos. 39 and 40; abstr., Centralbl. f. klin. Med. **8**: 469 (June 18) 1887
600,000	Puchberger, G.: Wien. med. Wchnschr. **55**: 1402, 1905
635,000	Brodie, T. G., and Russell, A. E.: J. Physiol. **24**: 360 (May 12) 1899
635,000	Zeller, H.: Ztschr. f. d. ges. exper. Med. **10**: 103, 1919-1920
760,000	Flössner, O.: Ztschr. f. Biol. **77**: 113, 1922-1923
778,000	Kemp, G. T., and Calhoun, H.: Brit. M. J. **2**: 1539 (Nov. 23) 1901
862,000	Kemp, G. T., and Calhoun, H.: Am. J. Physiol. **5**: 4, 1901

leukocytes or to the apparatus employed, particularly glassware. Numerous solutions have been proposed and used as preserving fluids. Solutions of many neutral salts, i. e., indifferent fluids, as of sodium chloride, magnesium sulphate, etc., have been employed. Various fixing reagents have been recommended, such as Hayem's fluid and Ferrier's fluid (consisting of alcohol, glycerin, fuchsin and water). Solutions of anticoagulants have been used a great deal, for example, solutions of citrates, oxalates, etc. Besides these, a great many solutions of organic substances, both of synthetic and of natural origin, have been advocated. Hypotonic, isotonic and hypertonic, hemolytic and non-hemolytic solutions have been tried and accepted or rejected by various investigators.

The preserving fluid, to be satisfactory, must first of all rapidly fix and preserve both the blood platelets and the erythrocytes. If not quickly fixed and preserved, the former tend to disintegrate promptly into coarse refractile granules, while the latter are apt to undergo

degenerative changes with the production of artefacts, usually in the form of "Arnold bodies." It must also prevent the sticking together of the platelets, for they must remain freely movable in the preparation in order to be easily identified when examined in clear solution. Furthermore, the preserving fluid must have a relatively low specific gravity, which will allow fairly rapid sedimentation of the platelets. Isotonicity of the preserving fluid is important, for when the diluting fluid is hypotonic or hypertonic artefacts are formed, usually from the erythrocytes, which may be mistaken for platelets, particularly when the ordinary counting chamber and high dry lens are used. When a direct or an indirect platelet count is made, bacteria, if present in the diluting fluid, often simulate platelets; it is therefore important to work with fairly stable solutions that do not become readily contaminated. A number of solutions proposed contain a dye that stains the platelets. These usually have the disadvantage of containing a fine precipitate which at times interferes with the platelet count.

With the oil immersion lens I examined, after filtering them, the solutions of Rees and Ecker,[4] Buckman and Hallisey[5] and Wright and Kinnicutt,[6] and found that each contained a fine precipitate that either obscured the field or was easily confused with platelets.

In this investigation, a 2 per cent solution of sodium metaphosphate was employed, as originally recommended by Pratt.[7] The solution has the following composition: sodium metaphosphate (Merck), 2; sodium chloride, 0.9; distilled water, 100.

In my experience, this solution has proved most satisfactory. It appears to keep almost indefinitely and rarely becomes contaminated with molds or bacteria. It has been kept without deterioration for over a year. In this preserving fluid, the platelets and erythrocytes are excellently preserved. The formation of "Arnold bodies" from erythrocytes is seen only in older preparations, and such bodies can be easily identified and differentiated from platelets when the oil immersion lens is employed. In this solution, the platelets appear as clear, highly refractile bodies surrounded by a halo of fine radiating lines. At times, they vary considerably in size, from one-fourth to one-half the diameter of a red cell. The smaller platelets are probably the younger ones.[3] If the preparation has been properly made, the platelets and erythrocytes

4. Rees, H. M., and Ecker, E. E.: An Improved Method for Counting Blood Platelets, J. A. M. A. **80**:621 (March 3) 1923.

5. Buckman, T., and Hallisey, J. E.: Studies in Properties of Blood Platelets, J. A. M. A. **76**:427 (Feb. 12) 1921.

6. Wright, J. H., and Kinnicutt, R.: A New Method for Counting Blood Platelets for Clinical Purposes, J. A. M. A. **56**:1457 (May 20) 1911.

7. Pratt, J. H.: A Critical Study of the Various Methods Employed for Enumeration of Blood Platelets, J. A. M. A. **45**:1999 (Dec. 30) 1905.

are never clumped, but are discrete and freely movable. No precipitate is formed to obscure the field or to be confused with the platelets. The specific gravity is relatively low, allowing rapid sedimentation of the platelets. It is inexpensive and easily prepared.

In the course of this investigation, it was thought desirable to make comparative studies by the technic to be described, with the following preserving fluids:

1. Kemp and Calhoun's solution,[8] composed of 1 part of 40 per cent formaldehyde solution and 15 parts of 1 per cent sodium chloride solution, tinged with either methyl green or methyl violet; the fluid is therefore approximately 2.5 per cent formaldehyde and 1 per cent sodium chloride. This solution acts as a good preservative, but only for a relatively short time; at the end of from fifteen to twenty minutes, numerous "Arnold bodies" appear in the preparations, either free or in the process of separation from the red cells. Employing the indirect method, Kemp and Calhoun determined the number of erythrocytes with the hematocrit, and the ratio of platelets to erythrocytes in a Thoma-Zeiss counting chamber. This method involves considerable error, owing to the employment of the counting chamber, for it permits the inclusion in the platelet count of "Arnold bodies," which are not readily differentiated from platelets when the high dry lens is used. In fact, Kemp[9] claimed that he saw platelets which contained hemoglobin and at times were attached to the red cells, these platelets being identical with Hayem's "globules nains." The latter investigator[10] believed that these small formations were hemoblasts, i. e., precursors of erythrocytes. In discussing Kemp's paper, which was presented before the Johns Hopkins Hospital Medical Society, Osler remarked: "I have spent many weary hours over them [referring to platelets], but I never caught one blushing." These blushing platelets were undoubtedly "Arnold bodies" which were mistaken for platelets. The average number of platelets per cubic millimeter, as indicated by a mean of seventy-five observations on nineteen different persons, was found by Kemp and Calhoun to be 778,000. In another series[11] of determinations, the average number of platelets per cubic millimeter based on fourteen different counts from eleven men and six different counts from two women was 862,000 for men and 833,000 for women. In still another

8. Kemp, G. T., and Calhoun, H.: Enumeration of Blood Platelets: Their Relation and that of the Leucocytes to Blood Coagulation, Brit. M. J. **2**:1539 (Nov. 23) 1901.

9. Kemp, G. T.: The Effect of Altitude on Blood Plates and Blood Corpuscles, Bull. Johns Hopkins Hosp. **15**:177 (May) 1904.

10. Hayem, G.: Du sang, Paris, 1889.

11. Kemp, G. T., and Calhoun, H.: Some New Observations on Blood Plates and Leucocytes, Am. J. Physiol. **5**:4, 1901.

study,[12] the mean of five counts on five consecutive days on the same person was 457,000 platelets per cubic millimeter. The high counts of these investigators were undoubtedly due to the inclusion in the platelet count of large numbers of "Arnold bodies." By employing my technic, which will be discussed later, I obtained comparative counts with Kemp and Calhoun's solution, as shown in table 2.

2. Fonio's solution.[13] This is a 14 per cent solution of magnesium sulphate. It is highly hypertonic, as seen from the crenated and shrunken appearance of the erythrocytes. Most preparations showed numerous artefacts in the form of "Arnold bodies." The preparations contained remarkably few small platelets, which were undoubtedly destroyed. Fonio employed the indirect method. By means of dry

TABLE 2.—*Normal Platelet Counts When the Author's Technic was Used with Kemp and Calhoun's Solution*

			Platelets per Cubic Millimeter	
Person	Sex	Age	Pratt's Solution	Kemp and Calhoun's Solution
46	M	30	796,000	278,000
47	M	29	979,000	449,000
48	M	27	652,000	208,000
49	M	28	662,000	224,000

TABLE 3.—*Normal Platelet Counts When the Author's Technic was Used with Fonio's Solution*

			Platelets per Cubic Millimeter	
Person	Sex	Age	Pratt's Solution	Fonio's Solution
55	M	28	765,000	404,000
56	F	22	741,000	276,000
57	F	40	614,000	468,000

preparations, he obtained average counts of 234,231 platelets per cubic millimeter. Comparative counts by my technic yielded results as shown in table 3.

3. Rees and Ecker's solution.[4] This solution consists of 3.8 per cent sodium citrate, 0.2 per cent formaldehyde and 0.1 per cent brilliant cresyl blue. The platelets and the red cells were not well preserved in this solution; the erythrocytes frequently appeared crenated, with many artefacts ("Arnold bodies") attached to them. The preparations frequently contained a fine precipitate that obscured the field. No figures

12. Kemp, G. T.: Relation of Blood Plates to the Increase in Number of Red Corpuscles at High Altitudes, Am. J. Physiol. **6**:11, 1902.

13. Fonio, A.: Ueber ein neues Verfahren der Blutplättchenzählung, Deutsche Ztschr. f. Chir. **117**:176 (June) 1912.

were given by the authors. By my technic, comparative counts yielded figures as shown in table 4.

4. Tyrode's Solution.[14] This solution, which is a good artificial nourishing fluid, has the following composition: Na CL 8; KCL 0.2; Ca Cl_2 0.1; NaH_2PO_4 0.05; $NaHCO_3$ 1; dextrose 1; oxygen to saturation, and H_2O 1,000.

Flössner[15] modified this solution by omitting the dextrose and oxygen and adding mercuric chloride in the proportion of 5 parts of Tyrode's solution to 1 part of a 1 per cent solution of mercuric chloride. Flössner's modification of Tyrode's solution is a good preservative, much better for erythrocytes, however, than for platelets. The latter are preserved for about twenty minutes; then they begin to disintegrate

TABLE 4.—*Platelet Counts When the Author's Technic was Used with Rees and Ecker's Solution*

			Platelets per Cubic Millimeter		
Person	Sex	Age	Pratt's Solution	Rees and Ecker's Solution	Remarks
58	M	58	969,000	507,000	Normal
59	M	23	437,000	259,000	Chronic secondary anemia
60	F	40	534,000	343,000	Normal

TABLE 5.—*Normal Platelet Counts When the Author's Technic was Used with Flössner's Solution*

			Platelets per Cubic Millimeter	
Person	Sex	Age	Pratt's Solution	Flössner's Solution
46	M	30	796,000	261,000
47	M	29	979,000	278,000
48	M	27	652,000	405,000
49	M	28	662,000	197,000

into rather coarse refractile granules. I found both Tyrode's original solution and Flössner's modified Tyrode's solution inferior to the solution of sodium metaphosphate. They have the added disadvantage of being much more complicated in composition. By employing the indirect method and a counting chamber, a procedure involving considerable error, Flössner[15] and Hoffmann[16] found that the average number of platelets per cubic millimeter based on seventy-five counts from twenty-five normal persons was 760,000 in men and 682,000 in women; the

14. Tyrode, M. V.: The Mode of Action of Some Purgative Salts, Arch. internat. de pharmacod. et de thérap. **20**:205, 1910.

15. Flössner, O.: Beobachtungen und Zählung von Blutplättchen, Ztschr. f. Biol. **77**:113, 1922-1923.

16. Hoffmann, F. B.: Ueber Blutplättchenzählung, Deutsche med. Wchnschr. **52**:861 (May 21) 1926.

maximum being 907,000 and the minimum 636,000. Table 5 shows the comparative counts obtained by the technic described in this paper.

ERRORS IN THE USE OF THE GRADUATED PIPET

The tendency of the platelets to adhere to glass and other foreign substances has been overlooked or disregarded by many in selecting a method for counting platelets. Halla,[17] Muir[18] and other early investigators recognized the fallacy of employing the graduated pipet. It is significant that, as a rule, when the capillary pipet was used by investigators the counts were lower than when some other method was employed which obviated the loss of platelets through their adherence to the sides of the pipet. This error, as Pratt [7] has shown, may amount to 50 per cent. The objections to the use of the graduated pipet have been emphasized by nearly all investigators of the subject, and those who have used it have pointed out that while the results are only approximately accurate, they are still of value. One variable factor in the error of this method is the temperature of the pipet, as has been recognized by Hayem [10] and by Kemp, Calhoun and Harris;[19] in a warm room, the error would be greater than in a cold room. No method, therefore, can be regarded as trustworthy, which involves the use of the graduated pipet.

ERRORS IN THE USE OF THE COUNTING CHAMBER

Many investigators have recognized that in the ordinary counting chamber foreign bodies might easily be mistaken for platelets; hence the unreliability of counts made in this manner. Even when the dry high power lens is used, products of degenerated erythrocytes ("Arnold bodies"), foreign particles and bacteria may be mistaken for platelets. The platelets themselves, particularly the small forms, are often recognized with difficulty in the chamber. Another objection to this procedure is the depth of the chamber, as was pointed out by Pratt,[7] Halla [17] and others. The ordinary Thoma-Zeiss chamber is 0.1 mm. or 100 microns deep, which is more than fifty times the diameter of the average platelet. The erythrocytes quickly settle to the bottom, but the platelets, being considerably lighter in weight, tend to float in the upper layers of the fluid and do not all settle to the bottom. It is therefore difficult not to miss some of them in the count. Even when specially constructed

17. Halla, A.: Ueber den Haemoglobingehalt des Blutes und die quantitativen Verhältnisse der rothen und weissen Blutkörperchen bei acuten fieberhaften Krankheiten, Ztschr. f. Heilk. **4**:331, 1883.

18. Muir, R.: Contributions to the Physiology and Pathology of the Blood, J. Anat. & Physiol. **25**:256 (Jan.) 1891.

19. Kemp, G. T.; Calhoun, H., and Harris, C. E.: The Blood Plates, Their Enumeration in Physiology and Pathology, J. A. M. A. **46**:1022 (April 7) 1906.

chambers with smaller depths are employed, methods involving their use are unreliable (Pratt,[7] Helber [20]).

THE AUTHOR'S PROCEDURE

In order to avoid the use of the graduated pipet and of the counting chamber, I employed the indirect method so modified that the freshly drawn blood comes in contact with only paraffin-coated surfaces. A drop of freshly drawn blood is transferred to a paraffin cup filled with the preserving fluid. A few small drops of the diluted blood are then placed on a cleaned glass slide and covered with a cover slip, and the ratio of the platelets to the red cells is determined. The number of erythrocytes is then counted with the ordinary Thoma-Zeiss apparatus.

Slides are placed first in strong sulphuric acid saturated with potassium bichromate, and are kept there from twenty-four to seventy-two hours; they are then washed in water and alcohol and placed in jars containing 95 per cent alcohol. They are removed from the alcohol and wiped dry immediately before use. The glassware must be scrupulously clean, for, as Fenn [21] showed, hemolysis is most marked on slightly soiled glass and may occur so rapidly with unfixed cells that accurate counts are rendered impossible. When hemolysis occurs, artefacts in the form of "Arnold bodies" nearly always appear.

TABLE 6.—*Comparison of the Platelet Counts of Blood from Finger and from Ear*

Person	Platelets per Cubic Millimeter	
	Finger	Ear
42	578,000	392,000
50	711,000	636,000
51	492,000	472,000
52	603,000	512,000

The site from which the blood is to be drawn must be thoroughly cleaned with soap and water and then with alcohol and ether immediately before the puncture is done. More elaborate preparation of the skin is unnecessary. In order to avoid contact of the freshly drawn blood with the skin, I have attempted to cover the site of the puncture with some inert substance and to puncture through it. Paraffin, paraffin dissolved in xylene and collodion dissolved in ether were tried, but the counts obtained were so unsatisfactory that I abandoned this additional procedure. Aynaud,[22] Buckman and Hallisey,[5] Kristenson [23] and others

20. Helber, E.: Ueber die Zählung der Blutplättchen im Blute des Menschen und ihr Verhalten bei pathologischen Zuständen, Deutsches Arch. f. klin. Med. **81**:316 (Sept.) 1904.

21. Fenn, W. O.: Hemolysis of Erythrocytes in Contact with Glass, J. Exper. Med. **35**:271 (Feb.) 1922.

22. Aynaud, M. N.: Le globulin des mammifères, Med. diss., Paris, 1909.

23. Kristenson, A.: A New Method for the Direct Counting of Blood Platelets, Acta med. Scandinav. **57**:301, 1922.

recommended venipuuncture, because by this procedure adhesion of platelets to raw surfaces and admixture of tissue juices are avoided. Besides being more inconvenient, this method does not yield higher counts than the methods in which capillary blood is used. Zeller [24] concluded from careful comparative studies that venous blood gives lower platelet counts than capillary blood. Because of the simplicity and the ease with which it is carried out, I have employed the method of simply stabbing the finger or lobe of an ear with a clean, sharp needle. The puncture should always be made sufficiently deep to cause the blood to flow freely without applying any pressure. The application of pressure adjacent to the puncture wound must always be avoided, as this procedure may reduce the normal platelet count to one-half its

TABLE 7.—*Normal Platelet Counts by the Author's Method*

Person	Age	Platelets per C.Mm.	Person	Age	Platelets per C.Mm.
		MALES			
1	33	502,000	38	17	453,000
2	30	506,000	41	15	672,000
3	32	717,000	43	55	531,000
5	30	673,000	44	24	776,000
6	27	705,000	45	35	598,000
8	27	407,000	46	34	796,000
9	35	699,000	47	30	979,000
10	38	614,000	48	27	652,000
19	35	414,000	49	30	662,000
20	69	668,000	50	27	711,000
21	30	571,000	51	55	492,000
29	30	741,000	52	25	603,000
30	30	539,000	54	58	1,108,000
32	32	431,000	55	28	765,000
33	34	478,000	58	58	969,000
37	35	733,000			
		FEMALES			
11	36	491,000	27	42	566,000
15	16	715,000	42	42	578,000
17	60	450,000	56	22	741,000
18	72	569,000	57	40	614,000
24	66	706,000	60	40	534,000
25	36	439,000	61	42	531,000
26	14	691,000			

value. Blood obtained from the fingertip gives higher platelet counts than blood obtained from the lobe of an ear, as shown in table 6.

Two or three large drops of the sodium metaphosphate solution are placed in a small paraffin cup. The cup can be prepared by melting the center of a small cube of paraffin, about 2 cm. on the side, with the heated end of a glass rod. A small drop of freshly drawn blood is allowed to fall into this solution, producing a dilution of approximately 1:10. This is gently stirred once or twice with an ordinary wooden applicator, the end of which is coated with paraffin. A few small drops or one large one of this mixture is transferred by means of the wooden applicator to a cleaned glass slide, covered with a cleaned cover slip

24. Zeller, H.: Neue Methode der Blutplättchenzählung nebst einigen Resultaten, Ztschr. f. d. ges. exper. Med. **10**:103, 1919-1920.

and sealed with petrolatum. Two preparations should always be made, and if the ratio of platelets to erythrocytes varies markedly in the two, new specimens should be prepared. An oil immersion lens should be used. A square diaphragm in the ocular facilitates counting; this can be made from thick paper or a card, and forms a simple substitute for Ehrlich's ocular. The platelets and erythrocytes are both counted in fields taken at random in different parts of the specimen, until at least from 250 to 500 red cells in each of the two preparations have been seen. A red cell count is then done in the usual manner, and the absolute number of platelets per cubic millimeter is determined.

Table 7 represents the platelet counts obtained by this method on forty-four normal persons, thirty-one males and thirteen females.

The minimum count in this group was 407,000 platelets per cubic millimeter; the maximum, 1,108,000. The average for the group was

TABLE 8.—*Variation of the Platelet Count of the Normal Adult*

Adult	Sex	Age	Date (1928)	Platelets per C.Mm.	Average	Percentage of Variation
1	M	27	June 20	705,000		
			Oct. 24	711,000	708,000	0.8
2	M	30	Aug. 6	539,000		
			Aug. 15	540,000	539,500	0.2
3	M	30	Aug. 2	741,000		
			Aug. 22	662,000	701,500	11.2
4	M	34	Aug. 10	478,000		
			Aug. 13	433,000	455,500	9.9
5	F	42	Sept. 28	566,000		
			Oct. 31	578,000	572,000	2.0

619,000 platelets per cubic millimeter; the average for males was 650,000; that for females was 587,000.

I observed that when the platelet count is below 500,000 per cubic millimeter, the platelets tend to be of the large or adult variety. This observation was also made by Boshamer.[3] In no. 8, whose platelet count was 407,000, the individual platelets were unusually large. The higher platelet counts of normal persons are due to the presence of numerous small forms, and it is probable that in these persons there is an unusually active formation of platelets.

In order to determine the variation of the platelet count of the same person, I made counts of blood from five healthy adults on different days, as shown in table 8.

In view of the physical properties of the platelets, particularly their fragility and light weight, it appears to me that differences up to 10 per cent or even 15 per cent should be considered as within the permissible errors of the method employed. The average percentage of variation in the group mentioned was 4.8 per cent.

Moderately high platelet counts were previously obtained by investigators as follows: Prus,[25] 500,000; Puchberger,[26] 600,000; Brodie and Russell,[27] 635,000; Zeller,[24] 635,000; Flössner,[15] 760,000; Sooy and Laurens,[28] from 762,000 to 863,000; Kemp and Calhoun,[29] 778,00 and 862,000. All these investigators, however, employed methods involving the use of either the graduated pipet or the counting chamber or of both. Their results are therefore untrustworthy. Zeller's method involves the use of a paraffin cup and torsion weights, a procedure not well adapted for clinical purposes. The results that can be considered as trustworthy are those obtained by the indirect methods for the enumeration of blood platelets and based on the determination of the erythrocyte-platelet ratio in fresh preparations, thereby obviating the necessity of the graduated pipet and of the counting chamber. Such methods were employed by Pratt,[7] von Boros and Kalstein[30] and Jedlička and Altschuller.[31] Their results are, however, lower than mine. Pratt,[7] who originally used the sodium metaphosphate-sodium

TABLE 9.—*Comparison of the Platelet Counts Done by the Author's and by Pratt's Technic*

Person	Sex	Age	Platelets per Cubic Millimeter	
			Author's Technic	Pratt's Technic
62	F	9	556,000	353,000
63	M	29	570,000	440,000
64	M	26	661,000	398,000

chloride solution employed in this investigation, obtained average counts of 469,000 platelets per cubic millimeter. His technic, however, was different and consisted of a transference of the freshly drawn blood to some preserving fluid on a glass slide by means of a sterilized platinum loop, filled with the same solution. Comparative studies done by the technic described here and by that of Pratt are shown in table 9.

25. Prus, J.: Einiges über das Verhalten des leukämischen Blutes, Medycyna, 1886, nos. 39 and 40; abstr., Centralbl. f. klin. Med. **8**:469 (June 18) 1887.

26. Puchberger, G.: Wien. med. Wchnschr. **55**:1402, 1905.

27. Brodie, T. G., and Russell, A. E.: The Enumeration of Blood Platelets, J. Physiol. **21**:390 (May 12) 1897.

28. Sooy, J. W., and Laurens, H.: A Method for Counting Blood Platelets, Proc. Soc. Exper. Biol. & Med. **22**:116, 1924.

29. Kemp and Calhoun (footnotes 8 and 11).

30. Von Boros, J., and Kalstein, O.: Ein Beitrag zur Frage der Blutplättchenzählung, Folia haemat. **35**:419, 1928.

31. Jedlička, V., and Altschuller, G.: Chronic Essential Thrombopenia, Acta med. Scandinav. **64**:123, 1926.

SUMMARY

An improved indirect method for the enumeration of platelets is described. It adheres to the leading principles that must be taken into consideration in counting platelets: (1) avoidance of contact between the undiluted blood and glassware or metal, (2) mixing of the freshly drawn blood as quickly as possible with the preserving fluid and (3) avoidance of all unnecessary manipulations of the blood. It dispenses with the use of the graduated pipet and counting chamber. It eliminates the errors resulting from the inclusion in the platelet count of degeneration products of erythrocytes ("Arnold bodies") and of finely particulated foreign matter. The results obtained are higher than ever previously obtained by similar methods.

TROPICAL SPRUE

EXPERIENCE WITH THIRTY-SIX CASES *

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According to Osler, it is difficult to classify sprue, as various views of its etiology are held. It is a disease of tropical or subtropical countries, more often occurring in the newcomer and in the better class of people. The disease is characterized by a distinctive sore tongue and mouth, a peculiar type of diarrhea, marked anemia, loss of weight and a tendency to remissions and exacerbations. Its etiology is unknown; various theories are given, some of which are pancreatic disease, mold, infection with *Monilia* or bacteria or deficiency in fat.

In this paper we shall deal more especially with the study of sprue as we have found it in thirty-six patients who have entered our clinic in the past five and one-half years. Most of these patients were missionaries, and most of them came from the Orient. There were sixteen patients from China, seven from India, five from Korea, four from the Philippines, two from Porto Rico, one from Costa Rica and one from Persia. Twenty-four of the patients were women, and twelve were men. None of the patients was under 32 years of age, and sixteen were from 40 to 60 years of age. The oldest was 71. All of these patients had been in the Orient or tropical countries from one to thirty-nine years and had contracted the disease after living for from a few months to thirty-eight years in the foreign country. One patient, after seventeen years' residence in the Philippines, returned to this country underweight and anemic, and typical symptoms of sprue with tetany developed three years later. Another patient, one year after returning to this country, developed symptoms of sprue following a severe infection from a spider bite.

Few autopsies on patients with sprue have been reported. Musgrave reported several cases from the Philippines, Rosenfeld one case, and Baumgartner and Thomas one from our clinic.[1] The marked loss of weight was evident in all cases described as well as the large, thin-walled, dilated colon, which in our case was filled with pasty, gray fecal matter from which *Monilia* was readily grown. The serosal linings, especially

* Submitted for publication, Feb. 28, 1930.

1. Baumgartner, E. A., and Thomas, W. S.: A Case of Tropical Sprue with Autopsy, Clifton M. Bull. **11**:90, 1925.

the peritoneum, were edematous and grayish, and enlarged mesenteric lymph nodes with no microscopic peculiarity were found in several cases. A careful search revealed in our patient only one parathyroid gland that was normal. No distinctive pathologic process was observed.

The earliest symptom has usually been diarrhea (twenty-five cases). Two patients complained first of weakness, two of loss of weight, three of a sore mouth, and one of fatigue. The diarrhea has almost always been characteristic for sprue, with large, frothy, grayish stools occurring some time in the course of the disease. The diarrhea frequently occurs in the early morning hours. Constipation is present at times, as shown in one patient who entered our clinic with a history of sprue of nine years' duration. Recently, marked constipation had developed, but there were other well marked symptoms of sprue. At some time all the patients had trouble with the mouth, consisting of definite small ulcers in most cases. Several complained of a severe burning sensation in the mouth, and in two cases there occurred a dry mouth, in one of which ulcers did not develop until three years after the first entry to the hospital. All of them complained of marked abdominal distention with much gas during the course of the disease, and two complained of severe burning of the stomach. One of these patients was successfully treated with daily lavage of the stomach, but in the other patient it was a difficult condition with which to deal. Eighteen patients gave histories of more or less tingling and numbness of the hands and feet, while four had definite signs of tetany. All the patients gave histories of weakness and of more or less loss of weight during the acute process.

There is nothing of particular interest in the previous illnesses of these patients except that five gave a history of amebic dysentery and four of malaria contracted during their stay in the tropics. Usually, after careful questioning, it was found that the diagnosis of dysentery or malaria was made at the onset of sprue, and this made it difficult to differentiate the symptoms of the conditions. These diagnoses of amebic dysentery and malaria were not verified at the time of the acute condition and often there was no typical history, such as bloody stools or typical chills and fever; hence we believe that probably these indicated only the onset of sprue.

Physically, these patients usually showed a considerable loss of weight, sallow skin, low blood pressure and a distended abdomen with a thin abdominal wall. Frequently the large bowel could be palpated, but the liver was not palpable nor was it especially small when carefully examined. In four cases the patients gave positive tetany reactions—Trousseau's and Chvostek's signs or tetany spasms. Ulcers of the mouth were seen frequently, appearing as small, white areas of from 2 to 3 mm. in width with reddened areas around them. These ulcers

were usually on the tongue, and sometimes the mucous membrane of the floor of the mouth or cheeks was involved. In one case a fiery inflammation of the mucosa of the mouth occurred while the patient was under observation. The loss of weight has been more than one fourth of the patient's average weight in fifteen patients, eleven of whom had severe anemia; of the four others with a history of severe loss of weight, one had a marked secondary anemia.

Various laboratory tests were carried out and frequently repeated. Examinations of the urine showed nothing particular, albumin, leukocytes and casts occurring in some specimens. The urobilogen and the urobilinogen were sometimes increased. Sugar was not found in any patient. The function of the kidney was impaired in the two oldest cases, but this condition improved under the diet high in protein.[2]

The feces were almost always characteristic of sprue during the acute process. One phase of our study of sprue has been the culture of stools for the monilia organism.[3] In twenty-three cases we were able to grow a monilia which corresponded in all characteristics with Ashford's *Monilia psilosis*. In nine cases, a yeast organism was grown that was somewhat atypical. In only three cases were no monilia found, and in many positive cultures they were repeatedly obtained. The organism was grown from material taken from the tongue in one of six cases in which such cultures were made. It was grown from various parts of the digestive tract from material obtained at autopsy in one case.[1]

In twelve cases there was a secondary anemia of more or less severe degree, and in eight cases the blood was normal. In sixteen there was a blood picture much like that found in pernicious anemia. In thirteen of these cases there were less than 3,000,000 red cells and in three there were less than 2,000,000. The color index was high, and there was a leukopenia. The percentage of lymphocytes was increased, that of the platelets decreased, and there were changes in the red cells such as poikilocytes, megalocytes and polychromatophilia. In these cases, however, we have rarely observed normoblasts, and megaloblasts were seen in only one.[4]

In the twenty-five patients tested, the blood sugar was normal, the blood urea and creatinine were disturbed only as the kidney was affected (nephritis, two cases); the blood cholesterol was normal in five cases, and the fatty acids possibly low in seven. Studies on the blood calcium

2. Baumgartner, E. A., and Hubbard, Roger S.: The Effect of High Protein Diet on Some Blood Constituents, Clifton M. Bull. **13**:52, 1927.

3. Baumgartner, E. A., and Smith, Glenn D.: The Monilia Psilosis as a Cause of Tropical Sprue, Am. J. Trop. Med. **6**:433, 1926.

4. Baumgartner, E. A., and Smith, Glenn D.: Pernicious Anemia and Tropical Sprue, Arch. Int. Med. **40**:203 (Aug.) 1927.

were carried out in many of our cases (thirty), and low values were found in eleven. In seven of these, the blood calcium was only slightly below normal (8.1 to 8.6), but in four the abnormality was marked. In one patient, while under observation, the blood calcium decreased from a normal to a markedly low figure, and with this decrease definite signs of tetany developed. The test for a toxic substance in the blood serum of patients with pernicious anemia, as developed by Macht,[5] has been tried in ten of our cases of sprue, six of which showed a blood picture like that found in pernicious anemia, and three of these showed the toxic substance present. After marked improvement in one of these cases this toxic substance was not found. A negative reaction to the test was obtained in the four cases of secondary anemia.

Gastric fractional studies showed achlorhydria in seven cases. There was also a negative alkaline tide in two cases; we have accepted these as belonging in the same group. These two cases and five of the seven of achlorhydria occurred among patients with a blood picture like that in pernicious anemia; two of the patients with secondary anemia showed achlorhydria. In the two cases in which the patients complained of severe burning of the stomach, there were normal acid curves in the fractional test.

Roentgen-ray studies of the gastro-intestinal tract were made in twenty-nine cases; dilated, atonic, gas-filled colons were found in thirteen. The haustrations in these colons were large and often irregularly spaced with some greatly dilated areas in which haustrations were entirely absent. Another feature that was prominent in the late cases was the apparent elongation of the colon; it appeared to fill the abdomen almost completely. The gas gave a peculiar mottled appearance to the colon as if it were mixed with the contents of the intestines, and there were often linear streaks of barium sulphate along the wall resembling those that are frequently seen in patients with colitis. The earlier cases of sprue showed these changes in a very mild degree or else not at all, but in the late cases the changes were exceedingly marked. We have also noticed that hypermotility often exists, with the head of the barium column reaching the lower part of the large bowel in a few hours, but in spite of this, some of the barium may remain in the colon for many days at a time. The advanced cases present such typical roentgen observations that one might almost suspect the presence of sprue from this factor alone, but in the earlier cases such studies give no clue to the presence of the disease.

5. Macht, D. I.: A Study of the Toxin of Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **23**:209, 1925; Pernicious Anemia, An Experimental Contribution to the Etiology, Diagnosis and Treatment, J. A. M. A. **89**:753 (Sept. 3) 1927.

DIAGNOSIS

From the preceding description of the history and physical examination we can see that when certain symptoms are present, the diagnosis of sprue is easy, but other cases occur in which the diagnosis may be difficult. In most cases the history of large, gray, frothy stools occurring in a patient having spent some time in the tropics should at least call to mind the possibility of sprue. If the diarrhea occurs in the early morning and is associated with sore mouth, weakness and loss of weight, sprue should be suspected. If, in addition to this, the abdomen is distended, small ulcers are present in the mouth, and there is a more or less severe anemia, the diagnosis of sprue may be made. Numbness and tingling may occur, but we have never found the neurologic signs of combined sclerosis such as those seen in pernicious anemia. In our experience, tetany and a low blood calcium, if they occur in cases showing such symptoms, make the diagnosis of sprue certain.

Two diseases, pancreatic deficiency and pernicious anemia, are especially likely to simulate sprue. Pancreatic disease may cause the large, gray foamy stools seen in patients with sprue, but the sore mouth does not occur, neither does one find the low blood calcium or a blood picture like that of severe pernicious anemia. Glycosuria, a not infrequent observation in pancreatic disease, was not seen once in our thirty-six cases of sprue. The differentiation between sprue and pernicious anemia is much more difficult; indeed, some authors, Wood [6] and Reed [7] among others, contend that they are one disease. The digestive disturbance, the sore tongue, the blood picture with megalocytes, the definite increase in the average size of the red blood cells such as Price-Jones found in pernicious anemia,[8] and the neurologic symptoms are very confusing. However, our patients with pernicious anemia rarely have early morning diarrhea, never the characteristic stools seen in sprue, nor such severe loss of weight, and never a low blood calcium nor tetany reactions. Two of the sixteen patients with a blood picture like that found in pernicious anemia had hyperchlorhydria. Only seven of the sixteen cases showed achlorhydria (two showed negative alkaline tides and were accepted as having achlorhydria). Three of these and also one with a normal hydrochloric acid content on fractional examination showed low blood calcium with tetanic reactions. One other patient with achlorhydria had 8.3 mg. of calcium per one hundred cubic centimeters

6. Wood, E. J.: Pernicious Anemia in Its Relationship to Sprue, Am. J. M. Sc. **159**:28, 1925.

7. Reed, A. C., and Wyckoff, H. A.: The Common Picture of Sprue, Pernicious Anemia, and Combined Degeneration, Am. J. Trop. Med. **6**:221, 1926.

8. Price-Jones, C.: Anisocytosis with Special Reference to Pernicious Anemia, Guy's Hosp. Rep. **74**:10, 1924.

of blood, which is lower than the normal figures for blood calcium. We feel that the roentgen examination of the digestive tract may be of distinct value in differentiating these two conditions. The dilated, atonic colon with much gas, often with no evidence of haustrations, is found in sprue and in our experience has not been seen in pernicious anemia. In five of seven patients showing achlorhydria, roentgen studies of the gastro-intestinal tract were not done; but two showed the colon typical of sprue. In the accompanying table are listed four

Data in Cases of Sprue with Blood Picture of Pernicious Anemia

Length of Illness, Years	Reaction of Blood, Pernicious Anemia Type	Fractional Free Acid	Gastro-intestinal Series	Tetany	Blood Calcium	Outcome of Cases	Diagnosis, Pernicious Anemia
3	Positive	Negative at autopsy	Not done	Positive	5.2	Death from sprue	No
9	Positive	0	Not done	0	8.3	Well 5 years	?
4	Positive	26	Sprue	Positive	6.2	Mental 4 years	No
6	Positive	Negative tide	Sprue	Positive	7.3	Death 1 year, sprue	No
1	Positive	34	Sprue	0	11.0	Death 5 years, later pneumonia	No
4	Positive	0	Sprue	Positive	3.1	?	No
10	Positive	0	Not done	0	10.3	Well 5 years	?
2½	Positive	21	Not done	0	10.4	?	No
3	Positive	68	Sprue	0	9.6	Well 3 years	No
2	Positive	47	Normal	0	10.7	Well 3 years	No
3	Positive	51	Normal	0	8.5	?	No
10	Positive	65	Sprue	0	8.6	Pneumonia, sprue 3 years	No
3	Positive	23	Sprue	0	10.0	?	No
3	Positive	34	Sprue	0	8.1	Well 1 year	No
1	Positive	0	Not done	0	10.8	Well 3 years	?
3	Positive	Negative tide	Not done	0	Not done	Well 2 years	?

cases in which we made the diagnosis of sprue but admit the possibility that they were cases of pernicious anemia. At times it is extraordinarily difficult, and even impossible to differentiate the two diseases, and we know of at least one patient who went through our clinic in the past five years with the diagnosis of pernicious anemia who undoubtedly had tropical sprue.

PROGNOSIS

Of the thirty-six patients whom we have considered, two were without symptoms and may be accepted as having arrested or "cured" cases for one and nine years. Five other patients had only mild symptoms, ten were moderately ill and nineteen were severely ill or completely incapacitated while under observation. One of the sixteen patients with a

blood picture like that found in severe pernicious anemia, died one week after entry, following a slight cold and pleurisy. Another patient left after several months' treatment with little if any improvement. Five months later this patient died with tetany spasms, evidently from sprue. In two severe cases, after improving markedly here, the patients died elsewhere from pneumonia, one five years, the other three years after his first entry here. Both of these had responded well to treatment, regaining weight and showing a normal blood picture, but both had relapses, from which one was again recovering, while the other showed no improvement in any of his symptoms. According to recent reports, eight of the remainder of the group of sixteen have been well physically for from one to four years, although one had a relapse two years ago from which she has again recovered. Four patients had not been heard from. In the other cases, it is reported that one patient died of a cancer of the digestive tract, six have not been heard from for two years, and the remainder have been well for from one to three years after discharge. One of the latter had a severe relapse but again recovered.

In the entire group only two patients failed to respond definitely and markedly to treatment. Three patients returned with exacerbations of some symptoms, but all responded to a more restricted diet than they had been using at home. Bastedo and Famulener,[9] in their study of sprue, described two patients who died of severe anemia and a color index of 1+. Reed stated that patients with sprue rarely recover.

TREATMENT

Our treatment for sprue has been mainly by a diet high in protein and low in fat and carbohydrates. Since Minot and Murphy's liver diet for pernicious anemia was described, we have used liver in some cases.[10] In our experience as well as in that of others liver has been as efficacious in the control of the anemia in cases of sprue as it has been in cases of pernicious anemia. Ashford [11] before the International Association of Tropical Medicine last year described some cases as being refractory to treatment with liver. One of our patients recently succumbed while under care in another hospital without having made any recovery in blood count, although three years previously he had gained from 2,000,000 to 4,800,000 erythrocytes in our clinic. Possibly

9. Bastedo, W. A., and Famulener, L. W.: Tropical Sprue, J. A. M. A. **81**:2102 (Dec. 22) 1923.

10. Rabe, Helen; and Baumgartner, E. A.: Diet in Tropical Sprue, Clifton M. Bull. **14**:55, 1928.

11. Ashford, B. K.: Suggestions for a Rapid Classification of the Anemias of Sprue, Porto Rico J. Pub. Health & Trop. Med. **5**:167, 1929.

this case could belong to Ashford's hypoplastic type of anemia. In one case with low blood calcium, Collip's parathyroid extract was given,[12] and in two others 1/10 grain (0.00648 Gm.) of the dry extract and 10 grains (0.648 Gm.) of calcium lactate, three times daily. In all of these patients the blood calcium quickly became normal, and the tetanic reactions disappeared. In one patient, however, who died one week after observation, the dry extract had no apparent effect as the blood calcium at autopsy was 5.6 mg. per hundred cubic centimeters of blood, which is about as it was at the onset of treatment. Another patient responded rather slowly to the administration of parathyroid (dry), but several months after leaving she did not respond at all to the intravenous injection of calcium chloride. Bovaird's patient, described by Barach and Murray,[13] also did not respond to intravenous injections of calcium. Details of the third case in our series, in which the patient died of pneumonia (and sprue), are not available. We wonder whether tetanic reactions might have been found, although during almost three years' observation of this patient, the blood calcium was only once found to be low (8.6 mg.), and there was no history of neurologic symptoms. Patients with achlorhydria, as well as those with pernicious anemia, are given dilute hydrochloric acid. This drug is quite difficult to take at times when ulcers or sore mouth are present. Pancreatic extract[14] has been given to several patients without any apparent effect. Transfusions have been used with good results when they were indicated.

SUMMARY

Thirty-six cases diagnosed as sprue have been reviewed. In sixteen of these the blood picture was similar to that in pernicious anemia; in all but four the condition could be conclusively shown not to be pernicious anemia (Addison), because free hydrochloric acid was found in the stomach, a low blood calcium with or without tetanic reactions was present, or a definitely large dilated colon occurred, which we believe is a characteristic of sprue and is not found in pernicious anemia. Several cases showed a severe secondary type of anemia. Improvement in the general physical condition with a definite return of the appetite almost always occurs with a restriction of carbohydrates and fats in the diet. Liver is valuable as treatment in the severely anemic cases frequently found.

12. Baumgartner, E. A.: Parathyroid in the Treatment of Tropical Sprue, Am. J. Trop. Med. **7**:181, 1927.

13. Barach, A. L., and Murray, H. A.: Tetany in a Case of Tropical Sprue, J. A. M. A. **74**:786 (March 20) 1920.

14. Brown, T. R.: Absence of Pancreatic Secretions in Sprue and Employment of Pancreatic Extract in Treatment of This Disease, Am. J. M. Sc. **161**:501, 1921.

THE ARTERIOVENOUS DIFFERENCE IN BLOOD SUGAR CONTENT *

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Since Claude Bernard [1] in 1877, Otto [2] in 1885 and Pavy [3] in 1894 showed that there is a difference in the sugar content of arterial and venous blood, greater during digestion, a number of workers have studied this aspect of sugar metabolism. There is general agreement that in the fasting state the arterial blood contains from 3 to 5 mg. per hundred cubic centimeters more sugar than the venous, and that after the administration of dextrose this difference is increased to between 20 and 80 mg. Lawrence [4] and Rabinowitch [5] found that in the patient with diabetes, the arteriovenous difference is very much reduced; in fact, in some cases the sugar in the venous blood is higher than in the arterial. Friedenson [6] gave a good historical review of the entire subject. It is obvious that the arteriovenous difference is due to the fact that the peripheral tissues, especially the muscles, either store or burn part of the dextrose that passes through them. Since Foster [7] showed that arterial blood and capillary blood are identical in sugar content, it is easy to determine the amount of dextrose removed from the circulating blood by measuring simultaneously the sugar content of capillary and venous blood. In this manner, probably information of important diagnostic value could be obtained; that is, information showing whether or not the peripheral tissues are able to metabolize dextrose in a normal manner. Yet a survey of the literature shows that there has been little effort to utilize the arteriovenous difference as an aid in clinical diagno-

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* From the Medical Service of the Jewish Hospital.

1. Bernard, Claude: Leçons sur le diabète, Paris, J. B. Baillière et fils, 1877, p. 237.

2. Otto, J. B.: Ueber der Gehalt des Blutes an Zucker und reducierender Substanz und verscheidenen Umständen, Pflüger's Arch. f. d. ges. Physiol. **35**:495, 1885.

3. Pavy, F. W.: Physiology of the Carbohydrates, London, J. & A. Churchill, 1894, p. 168.

4. Lawrence, R. D.: Effect of Insulin on the Sugar Content of Arterial and Venous Blood in Diabetics, Brit. M. J. **1**:516, 1924.

5. Rabinowitch, I. M.: Simultaneous Determination of Arterial and Venous Blood Sugar in Diabetic Individuals, Brit. J. Exper. Path. **8**:76, 1927.

6. Friedenson, W.; Rosenbaum, M. K.; Thalheimer, E. J., and Peters, J. P.: Cutaneous and Venous Blood Sugar Curves, J. Biol. Chem. **80**: 269, 1928.

7. Foster, G. L.: Studies on Carbohydrate Metabolism, J. Biol. Chem. **55**:291, 1923.

sis. It was the purpose in the experiments reported in this paper to study this aspect of the arteriovenous difference.

The tests consisted in the administration of 1.75 Gm. of dextrose per kilogram of body weight to patients without food for the preceding fifteen hours and confined to their beds, except in a few cases, for the duration of the test. A moderate quantity (from 400 to 800 cc.) of water was consumed during the period of observation. Capillary (arterial) blood from the finger pad and venous blood from the cubital vein

TABLE 1.—*Normal Persons: Sugar Content of Capillary and Venous Blood Following a Standard Dextrose Meal*

		Before Administration of Dextrose	After the Administration of Dextrose							
			½ Hour		1 Hour		2 Hours		3 Hours	
No.	Origin of Blood	Mg. True Sugar per 100 Cc. of Blood	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference
1	Arterial	101	173		158		128		110	
	Venous	88	114	+59	100	+58	100	+28	84	+26
2	Arterial	83	180		113		115		77	
	Venous	81	130	+50	97	+16	98	+17	71	+ 6
3	Arterial	80	105		113		93		69	
	Venous	72	83	+22	65	+48	56	+37	57	+12
4	Arterial	80	152		133		115		106	
	Venous	74	104	+48	98	+35	83	+32	73	+33
5	Arterial	75	158		102		127		101	
	Venous	82	113	+45	...	....	122	+ 5	95	+ 6
6	Arterial	94	166		152		121		99	
	Venous	88	138	+28	122	+30	83	+39	86	+13
7	Arterial	69	159		182		134		45	
	Venous	64	135	+24	161	+21	111	+23	40	+ 5
8	Arterial	83	154		154		139		106	
	Venous	89	150	+ 4	135	+19	...	....	96	+10
9	Arterial	93	154		207		178		120	
	Venous	94	144	+10	192	+15	166	+12	103	+17
10	Arterial	81	154		216		198		131	
	Venous	80	138	+16	184	+32	168	+30	106	+25
11	Arterial	84	176		207		121		67	
	Venous	90	160	+16	172	+35	97	+24	52	+15
12	Arterial	82	126		150		116		95	
	Venous	79	98	+28	107	+43	77	+39	60	+25

were obtained simultaneously before and at intervals after the administration of the dextrose. The true (fermentable) sugar (as distinguished from the total reducing substances) was determined according to Somogyi's (1929) technic. The figures given in the tables represent averages of three parallel determinations which agreed within ±6 mg. per hundred cubic centimeters.

Table 1 comprises twelve cases considered as normal, because from the history and the physical and laboratory examinations, no evidence of disturbed carbohydrate metabolism was discovered. An analysis of the figures discloses the following facts: 1. In fasting, there were but

slight differences between the sugar content of arterial and of venous blood. 2. The arteriovenous difference rises and recedes parallel with the blood sugar levels; its maximum occurs at the peak of the sugar curve thirty minutes after the ingestion of sugar in cases 1, 2, 4, 5 and 7, and at the one hour period in cases 3, 8, 9, 10, 11 and 12. Case 6 is the sole exception in which the maximal difference appeared two hours after the dextrose meal, whereas the sugar curve had risen to its peak in thirty minutes. 3. The maximum arteriovenous difference lies between 20 and 60 mg. per hundred cubic centimeters of blood. 4. These figures also disclose a fact of immediate practical significance; namely, that the blood sugar curves obtained from capillary blood cannot and

TABLE 2.—*Diseased Nondiabetic Persons: Sugar Content of Capillary and Venous Blood Following a Standard Dextrose Meal*

		Before Administration of Dextrose		After the Administration of Dextrose							
				½ Hour		1 Hour		2 Hours		3 Hours	
No. Diagnosis	Origin of Blood	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference
1. Hypothyroidism	Arterial	79		147		165		126		99	
	Venous	75	+ 4	124	+23	128	+37	117	+ 9	84	+15
2. Hypothyroidism	Arterial	84		160		177		164		123	
	Venous	77	+ 7	126	+34	137	+40	124	+40	89	+34
3. Hypothyroidism	Arterial	84		142		200		131		106	
	Venous	84	± 0	133	+ 9	174	+26	124	+ 7	78	+28
4. Hypopituitarism	Arterial	93		159		175		112		121	
	Venous	93	± 0	156	+ 3	162	+13	88	+24	97	+24
5. Chronic myocarditis	Arterial	85		167		193		169		146	
	Venous	80	+ 5	154	+13	175	+18	167	+ 2	127	+19
6. Duodenal ulcer	Arterial	87		245		299		192		138	
	Venous	92	— 5	221	+24	279	+20	160	+32	106	+32
7. Malnutrition	Arterial	96		152		187		157		151	
	Venous	..	....	139	+13	165	+22	134	+23	128	+23

should not be substituted indiscriminately for venous curves. At present, in the possession of several good micromethods for sugar determination, one is much inclined to avoid the inconveniences of five venipunctures, and instead to draw but a few drops of capillary blood from the finger tip. Considering the possible arteriovenous differences at the end of the curve, it is obvious that the application of standards based on figures of venous blood might lead to confusion if applied to results obtained from capillary blood.

In table 2 are presented the experiments in seven nondiabetic cases in which either various endocrine dysfunctions were diagnosed clinically or disturbed carbohydrate metabolism was indicated by laboratory tests. The first three patients suffered from hypothyroidism. The peak of the curves was within normal limits, and in two cases the maximal arterio-

venous difference was reached at one hour. However, the difference was prolonged, still being considerable at the three hour period, an observation not incompatible with that observed in the normal cases. In case 4, diagnosed as hypopituitarism, the maximal height of the venous sugar was reached in one hour, while the maximum arteriovenous difference was attained only after two hours and was maintained into the third hour. Cases 5 (chronic myocarditis) and 6 (duodenal ulcer) were examined, because it was thought that they would show a normal sugar metabolism. Surprisingly, the third hour level failed to drop to the fasting level. Case 5 showed a decided fluctuation in the arteriovenous difference, which was still high at the third hour. Case 6 showed an increasing arteriovenous difference, which was highest at the

TABLE 3.—*Diabetic Persons: Sugar Content of Capillary and Venous Blood Following a Standard Dextrose Meal*

		Before Administration of Dextrose		After the Administration of Dextrose							
				½ Hour		1 Hour		2 Hours		3 Hours	
No.	Origin of Blood	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference
1	Arterial	101		172		193		200		181	
	Venous	93	+ 8	156	+16	173	+24	176	+24	152	+29
2	Arterial	128		221		290		262		158	
	Venous	136	— 8	226	— 5	264	+26	255	+ 7	151	+ 7
3	Arterial	321		391		400		456		507	
	Venous	306	+15	369	+22	399	+ 1	441	+15	498	+ 9
4	Arterial	224		329		382		454		392	
	Venous	222	+ 2	316	+13	376	+ 6	437	+17	400	— 8
5	Arterial	172		294		368		422		430	
	Venous	173	— 1	292	+ 2	374	— 6	414	+ 8	435	— 5
6	Arterial	236		317		450		506		452	
	Venous	229	+ 6	321	— 4	449	+ 1	513	— 7	447	+ 5

second and third hours. In case 7, diagnosed as chronic malnutrition, both the arterial and the venous curves rose and fell slowly. The rather low arteriovenous difference persisted practically unchanged over the entire three hour period.

It is obvious in this group of cases, too, that the blood sugar curve obtained with capillary blood cannot be interpreted on the basis of so-called standard curves obtained with venous blood. It is also seen in the three cases of hypothyroidism that there is no curve characteristic of the condition, based either on arterial or venous blood sugar or on the arteriovenous difference.

The six cases given in table 3 are those of patients with diabetes. The most conspicuous fact disclosed by these figures is that, in conformity with Rabinowitch's data, the arteriovenous difference was con-

siderably lower than in the normal cases, and its occurrence was nearly without relation to the height of the sugar level. The greatest difference, 29 mg. per hundred cubic centimeters, found in case 1, occurred at the third hour; case 2 is the only one in which the maximal difference coincided with the peak of the curve. In cases 5 and 6, the arteriovenous differences were practically negligible, indicating a total lack of dextrose utilization in the peripheral muscles. Further studies are necessary to determine whether such patients are to be classified as totally diabetic, and whether the magnitude of the arteriovenous difference can furnish a better measure for the classification of diabetic patients than the simple blood sugar curves of venous or arterial blood alone.

SUMMARY

After ingestion of 100 Gm. of dextrose, the arteriovenous difference in blood sugar content showed such wide maximal variations (from 2 to 60 mg. per hundred cubic centimeters) that no normal standard could be predicated.

In a small number of diseased but nondiabetic persons studied, the maximal arteriovenous blood sugar differences (from 19 to 40 mg. per hundred cubic centimeters) were in the lower half of the range determined for normal persons.

In three of six patients with diabetes studied, the maximal arteriovenous blood sugar difference lay just within the lower limits of the normal range. In the other three, it was definitely reduced.

It would seem unjustified, on the basis of present knowledge, to attach a diagnostic significance to the arteriovenous difference in blood sugar content. It remains to be determined whether diabetic patients can be regrouped into two therapeutic or prognostic groups depending on whether the arteriovenous difference in blood sugar content lies within or below the range determined as normal.

THE NATURE OF GRAVES' DISEASE*

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NOSOLOGY

Conventionally, Graves' disease is viewed as a disease in which the predominant signs and symptoms are tremor, tachycardia, enlargement of the thyroid gland and exophthalmos. Of lesser importance are loss of weight, diarrhea and sweating, pigmentation, a relative lymphocytosis and, in severe cases, fever and jaundice. It is generally agreed that such patients are "nervous," irritable and restless, and that they sleep poorly. As a rule, the disease is accompanied by an increased basal metabolism.

The diagnosis of Graves' disease is simple when the cardinal signs are present. Clinically, however, one meets patients in whom one or the other of these signs is absent; for instance, one frequently sees patients with tremor, tachycardia and enlarged thyroid gland without exophthalmos (23.2 per cent, Sattler [1]) and others with tremor, tachycardia and exophthalmos but without an enlargement of the thyroid. Nevertheless, clinicians have tacitly included such patients within the province of Graves' disease. Difficulty enters as to the strict nosologic status of the exceedingly common group of patients who present all the classic evidences of the neuropathy of Graves' disease but who show little of the physical evidences except perhaps a tachycardia and a tremor. These patients are sensitive, emotional, anxious, tense and irritable. These are the cases that have been diagnosed variously as formes frustes, autonomic imbalance (Hyman and Kessel [2]), "Basedowoid" (Stern [3]) and "pre-Basedow" (Zondek and Bansi [4]). During the World War, a certain proportion of the patients whose cases were diagnosed as "neurocirculatory asthenia" presented these phenomena. The matter is further complicated by the fact that the clinical picture of formes frustes, etc., is not sharply drawn. For instance, Freidlander and Freyhof [5] reported that in 20 per cent of their cases of "neurocirculatory

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2. Hyman, H. T., and Kessel, Leo: Exophthalmic Goiter (Graves' Syndrome) and Involuntary Nervous System, J. A. M. A. **85**:1017 (Oct. 3) 1925.
3. Stern: Jahrb. f. Psychiat. u. Neurol. **39**:180, 1909.
4. Zondek, H., and Bansi, H. W.: Klin. Wchnschr. **8**:1697, 1929.
5. Friedlander, Alfred, and Freyhof, W. L.: Intensive Study of Fifty Cases of Neurocirculatory Asthenia, Arch. Int. Med. **22**:693 (Dec.) 1918.

asthenia" there was thyroid swelling, and in 6 per cent exophthalmos, while Lewis [6] found a swelling of the thyroid gland in 4 per cent. Brooks [7] found thyroid swelling in two thirds of his cases of neurocirculatory asthenia, especially in those of long duration; in such instances, also, he found exophthalmos. Addis and Kerr [8] found that patients with all the clinical evidences of neurocirculatory asthenia had an enlarged thyroid in about half the instances, although they believed that many of these enlarged thyroids were of an endemic origin. In civil life one sees the counterpart of this picture in the "neurotic" young woman whose pulse is consistently rapid and whose thyroid swells at every menses or during emotional stress and in "neurotic" men during periods of emotional crisis. Between this primitive type and the complete end-product, with the quadrad of cardinal symptoms, including the increased basal metabolism, one finds an almost endless variety of clinical combinations: tachycardia, tremor and enlarged thyroid without exophthalmos; tachycardia, tremor and exophthalmos without an enlarged thyroid; enlarged thyroid and elevated basal metabolism rate but without exophthalmos; increased basal metabolism without thyroid enlargement, etc.; but there is one common denominator in the vast majority of these combinations of clinical signs, the neuropathic personality already described. Despite the strong resemblance between this incomplete or aberrant picture and the finished product represented by the term Graves' disease, the majority of clinicians have been unwilling to regard the formes frustes as related to Graves' disease, and the reasons therefore are various. Carroll [9] held that some types of neurocirculatory asthenia and hyperthyroidism are identical. Barr [10] regarded neurocirculatory asthenia as a form of Graves' disease. Nevertheless, Grant,[11] in a five year follow-up of neurocirculatory asthenia, found that none of the patients had developed the fully fledged form of Graves' disease.

The issue of classification depends, as in so many provinces in medicine, on the interpretation of disease from the biologic rather than from the static point of view. In analyzing the opinions on this matter, one deduction becomes clear, namely, that most physicians regard the disease at the time of observation as having reached its fullest development and not merely as one phase of a process the natural history of

6. Lewis, Thomas: Soldier's Heart and the Effort Syndrome, New York, Paul B. Hoeber, Inc., 1919.

7. Brooks, H.: Am. J. M. Sc. **156**:726, 1918.

8. Addis, Thomas, and Kerr, W. J.: The Relative Frequency in Recruits With and Without Thyroid Enlargement of Certain Signs and Symptoms Which Occur in Neurocirculatory Asthenia, Arch. Int. Med. **23**:316 (March) 1919.

9. Carroll, J. H.: Am. J. M. Sc. **158**:35, 1919.

10. Barr, J.: Brit. M. J. **1**:544, 1916.

11. Grant, R. T.: Heart **12**:121, 1925-1926.

which extended long before and projected long after the period of observation. To classify a malady on signs that are subject to change is entirely artificial and misleading. One might as well regard the tadpole as an animal different from the frog.

It is becoming increasingly apparent that in order to be able to classify diseases on a sound biologic basis, one must observe disease over a far greater period than one has been accustomed to think. There are probably many maladies regarded as distinct species, which are in reality merely stages of disease processes that have thus far received different names and the relation of which is still unsuspected. Such observations are obviously more within the scope of the practitioner than of those who work in institutions or as consultants.

I had the fortunate experience of having witnessed the development of classic Graves' disease in a number of patients whom I had known and observed many years before. In no instance were the patients normal. They were sensitive, sanguine, quick, restless, temperamental, overstimulated and emotionally unstable, with bright eyes, and they invariably had rapid pulses and slight tremors which increased in periods of mental strain or emotional crisis. Their bowels moved under even slight emotion. These people were unusually slender. In other words, they corresponded precisely to the formula described by others as formes frustes, autonomic imbalance, basedowoid or pre-basedow. Their basal metabolism is within the normal range, but usually veers toward the plus side. The transition to the true Graves' disease, which is fairly sudden and often dates from some psychic insult, is characterized by an exaggeration of the tremor and the tachycardia; with these come abnormal sweating, loss of weight and often gastro-intestinal disturbances, with diarrhea or vomiting; soon a thyroid swelling appears, and the last important sign to develop is exophthalmos and its other attendant ocular phenomena. The basal metabolism is usually well toward the plus side. The classic clinical picture of Graves' disease is then complete.

The most interesting story in the evolution of this disease comes if the patient responds to whatever treatment is prescribed. The basal metabolism decreases more rapidly when subtotal thyroidectomy is performed than after medical treatment, because the thyroid gland is responsible for 40 per cent of the bodily heat (Dubois [12]). The patient gains weight, the pulse rate drops and the tremor subsides. The last symptom to disappear is the exophthalmos; it often persists throughout life. However, that which never disappears is the personality of the patient. The patient is still sensitive, emotional, restless, temperamental, sanguine, etc. Indeed, in this sense, the patient with Graves' disease

12. Dubois: Basal Metabolism in Health and Disease, Philadelphia, 1927.

is never completely cured, although he may be socially and economically restored. In fact, even in this condition, the patient is liable to greater or lesser recurrences of the disease, subject largely to his environmental adjustment. The other sequelae of Graves' disease are various and need not be discussed fully. Death from thyrotoxicosis, so called, is rare, and may occur at its inception or after any recurrence. Other persons become frank cardiac patients, as the result of the development of various arrhythmias (usually auricular fibrillation), cardiac hypertrophy from the persistent tachycardia and consequent increased volume output or the development of hypertension and its consequent cardiovascular phenomena. Death from cardiac insufficiency is late, often twenty years after the onset of the first signs of Graves' disease. I have witnessed a number of instances of the development of cardiac disease in patients who never passed beyond the stages of formes frustes. Once cardiac disease has developed, it is extremely difficult to cure by any of the recognized methods of therapy, but in a number of instances I have seen auricular fibrillation disappear after a subtotal thyroidectomy.

The point that I wish to make is that Graves' disease has a natural history, that its beginnings long antedate the full-blown clinical form, that its evolution is various and that in order to interpret this evolution, observations extending over many years, often throughout the life-time of the afflicted person, are necessary. It is incumbent on physicians, therefore, to be far more elastic in evaluating the criteria of diagnosis than they have been in the past; as shall be seen, it is rather in the summation of the various disease processes than in the rigid establishment of one or more criteria that the diagnosis is rendered possible. Certain of these criteria will be discussed later. It is for this reason that the term "syndrome" is more applicable in this connection than the term "disease," and so I shall call it henceforth.

Graves' syndrome, however, is not merely a combination of signs and symptoms. The study of this disease has convinced me that there is a common denominator, namely, the personality I have already described, which has been termed formes frustes, "basedowoid" and autonomic imbalance. There is no doubt in my mind that this personality is not the result of the disease, as some aver. In terms of modern usage, this personality may be termed part of the constitution of the disorder, although how far this personality is the result of environmental or of anatomic factors still requires extensive study.

THE CONSTITUTIONAL FACTOR IN GRAVES' SYNDROME

I have tried to show that if the patient is studied before the onset of the Graves' syndrome or if his personality is reconstructed afterward, he will conform to a class of individuals that may be described

in general terms as the sensitive emotional type, and furthermore, that no matter what kind of treatment is instituted, his personality persists although all other evidences of the disease have been eliminated. There is no physical make-up that is characteristic of the disease, for it occurs in persons of every variety of build. These people are touchy and extraordinarily sensitive to their environment. A look, a harsh word or a hostile attitude will upset them deeply and often irrevocably. As a consequence they are usually intolerant. They blush, sweat and become pale easily. In consequence of this unusual sensitiveness, they are apt to be shy and introverted. They are extraordinarily unstable in their emotivity, so that their moments of ecstasy and depression are widely removed. The curve of their mental life has wider excursions than that of the phlegmatic person, which is comparatively flat. They are quick and hasty in their movements and thoughts and are frequently irascible. They are sanguine and temperamental. They are prolific day dreamers, and ideation plays a large rôle in their mental life. Many of those who are described as having the "artistic" temperament belong to this group of persons. They are especially sensitive to thyroid preparations, while their opposites, the phlegmatic type, usually are not. They are usually bad sleepers. An exceedingly common observation is the history of "nervous" diarrhea following any emotional upset, such as a school examination, untoward news or a fright. Also, under such circumstances, the pulse quickens and there is trembling. Their powers of concentration are limited, and they become tired easily, both mentally and physically.

This type of person, in his main essentials, has been recognized ever since Charcot [13] gave an excellent description, but it is only in recent years that its relation to constitution has been recognized. Kocher [14] and Chvostek [15] summarized the type as belonging to the sanguine temperament. Oswald described this type as especially sensitive to thyroid medication, iodine and roentgenization of the thyroid, and as the frequent precursor of Graves' disease. Stern,[3] who invented the term "basedowoid," while appreciating the similarity to Graves' disease, nevertheless differentiated "basedowoid" from the latter on such artificial grounds as the greater severity and the more acute onset of Graves' disease. Bauer [16] was probably the first to place this predisposing type of person formally within the category of the constitutional diseases.

13. Charcot, quoted by Chvostek: Morbus Basedow und die Hyperthyrosen, Berlin, 1917.

14. Kocher: Arch. f. klin. Chir. **92**:677, 1910.

15. Chvostek: Morbus Basedow und die Hyperthyreosen, Berlin, Julius Springer, 1917.

16. Bauer: Die konstitutionelle Disposition zu inneren Krankheiten, Berlin, Julius Springer, 1921.

He acknowledged that under certain noxa (fear, infections, etc.) persons with such constitutions may develop Graves' disease, and brought in the vegetative nervous system, in which the thyroid is inserted as a "multiplicator" to explain most of the phenomena. Warthin [17] described this constitution perfectly, but, accepting the anatomic interpretation, he expressed the belief that this constitution has a constant anatomic substratum, namely, a thymicolymphatic hyperplasia, evidences of which are seen in the constant presence of hyperplastic lymph nodules in the thyroid, the presence of an enlarged thymus, etc.

Admitting, as all evidence seems to show, that a constitutional factor forms the background of Graves' disease, the matter is by no means settled by merely giving a label. The word constitution has a wide connotation, especially in respect to how far the elements forming such a constitution are congenital, hereditary or acquired.

RELATION OF GRAVES' SYNDROME TO HEREDITY

In Graves' syndrome the family history is highly illuminating. Most clinicians with considerable experience in Graves' syndrome have noted its occasional occurence in two or more members of the same family. I have seen a number of such instances. Sattler,[1] in his exhaustive monograph, reported many. Buschan,[18] Lerrede and Drouet,[19] Moss,[20] Bauer,[16] Chvostek,[15] Falta [21] and numerous others reported instances. Souques and Lermoyez [22] reported seven cases of Graves' syndrome in sixteen adults of one family covering three generations. This familial tendency is so common that it may be considered as occurring more frequently than the mere laws of chance would determine. Less frequently, Graves' disease has been reported as occurring in mother and child (Sattler [1]), Bauer,[16] Lenz.[23]

Of far greater import than the exposure of a familial or a hereditary tendency of the full-fledged Graves' syndrome is the revelation that the study of the relatives of the patients with this disease affords in appreciating the constitutional factor. In the instances in which I have had the opportunity to study such families, I have invariably found that the immediate relatives are what has been poorly termed "neurotic." They possess many or all of the characteristics that have been described as belonging to the constitutional type. They are "nervous," sensitive

17. Warthin: Ann. Int. Med. **2**:553, 1928.
18. Buschan: Die Basedowische Krankheit, Leipzig and Vienna, 1894.
19. Lerrede and Drouet: Bull. Soc. franç. de dermat. et syph. **28**:142, 1921.
20. Moss: New York M. J. **99**:482, 1914.
21. Falta: Handbuch der inneren Medizin, 1927, vol. 4, second part
22. Souques, A., and Lermoyez, J.: Rev. neurol. **35**:20, 1919.
23. Lenz: Arch. f. Rassen- u. Gesellsch.-Biol. **13**:1, 1918.

and high-strung; many have passed through "nervous breakdowns"; anxiety neuroses, hypochondriasis and psychasthenias are common; even true hysteria and psychoses are encountered.

This familial constitutional tendency has been noted frequently before. Charcot [15] first called attention to this neuropathic tendency. Numerous similar observations are reported in Sattler's monograph, in Bauer's monumental work on the "Constitution" and by Ostwald,[24] Pässler,[25] Holst,[26] Barker,[27] Falta,[21] Biedl [28] and Buschan.[18]

The observations on patients with neurocirculatory asthenia frequently bring to light a family history of a neuropathic tendency (Robey and Boas,[29] Oppenheimer and Rothschild,[30] Brooks,[7] Neuhof [31]). Lenz expressed the belief that this tendency is transmitted according to the Mendelian law. This constitution becomes apparent at a very early age, usually just at or before the period of puberty.

There is no doubt in my mind that this constitution is a familial trait. Is it congenital and hereditary in the sense that a gene is transmitted or is it acquired? Holst [26] expressed the belief that it is congenital, in the sense that there is a disturbance in the anlage of the nervous and the endocrine system. Warthin,[17] who said that the thymicolymphatic anatomic basis is the potential of this constitution, naturally believes it a congenital trait.

I believe that in the light of the modern study of the effect of environment on psychologic characteristics, it would be rash to jump too quickly to the conclusion that because a disease is familial and even hereditary it is congenital and transmissible. Here one is again confronted with the ancient controversy among biologists as to whether or not acquired characteristics, of which the constitution mostly consists, are transmissible. Certainly the burden of proof thus far rests with those who say that they are. Admitting, however, that part of the constitution is congenital, as in Warthin's sense, there is no doubt that the psychologic aspects in this constitution are affected profoundly by

24. Ostwald: München. med. Wchnschr. **27**:907, 1915.

25. Pässler: Deutsche Ztschr. f. Nervenh. **6**:210, 1895.

26. Holst: Acta chir. Scandinav., 1923-1924, suppl. 4.

27. Barker, L. F.: Nervous and Mental Symptoms in Exophthalmic Goiter, J. A. M. A. **71**:327 (Aug. 3) 1918.

28. Biedl: The Internal Secretory Organs, New York, William Wood & Company, 1913.

29. Robey, W. H., and Boas, E. P.: Neurocirculatory Asthenia, J. A. M. A. **71**:525 (Aug. 17) 1918.

30. Oppenheimer, B. S., and Rothschild, M. A.: The Psychoneurotic Factor in the Irritable Heart of Soldiers, J. A. M. A. **70**:1919 (June 22) 1918.

31. Neuhof, S.: The Irritable Heart in General Practice, Arch. Int. Med. **24**:51 (July) 1919.

environmental factors, in most instances by the influence of parents on children. In two instances of families in which Graves' syndrome occurred, the neuropathic constitution was directly traceable to a high-strung, sensitive, intolerant and extremely ambitious mother. In another, it was the result of a fussy mother with an anxiety neurosis, who so petted and shielded her brood in infancy and childhood that when the children reached the age of discretion they were unable to cope with the ordinary tribulations of everyday life.

THE RELATION OF THE THYMUS TO GRAVES' SYNDROME

Warthin's observations bring up the important relation between the thymus and Graves' syndrome. The frequent association of Graves' disease and enlarged thymus has been emphasized repeatedly. According to Seelig,[32] an enlarged thymus is found in from about 80 to 90 per cent of fatal cases of Graves' disease, while Haberer found a large thymus in 100 per cent of those dying from operation. Kocher [14] found an enlarged thymus in about 50 per cent, and Hammer [33] in about 63 per cent of all patients with Graves' syndrome. In Mount Sinai Hospital, New York, a large thymus was found in 95 per cent of fatal cases of Graves' syndrome. The enormous incidence of the thymicolymphatic constitution in this syndrome means something, and calls for an answer to the following questions: 1. How far does the thyroid affect the thymus? 2. How far does the thymus affect the thyroid gland? 3. Is there a relationship between these organs, and are their diseases therefore the simultaneous reactions to the same insult? 4. Is it possible for the thymus gland to undergo involution and then regenerate? 5. Are the lymphatic infiltrations within the thyroid gland so commonly present in Graves' syndrome evidences of a thymicolymphatic constitution or are they the result of some other factor, for instance, inflammation? Some of these questions can be answered quickly. That the thymus does not activate the thyroid gland in Graves' syndrome is shown by the fact that an enlarged thymus is exceedingly common without Graves' syndrome and that the lymphocytosis, which all agree is a symptom of the thymic constitution, persists after thyroidectomy (Chvostek [15]). That the thyroid gland does not necessarily cause hyperplasia of the thymus is shown by the fact that Graves' syndrome is common without any evidence of thymic enlargement.

That Graves' syndrome and thymic enlargement are not simultaneous reactions to the same insult is shown by the frequency with which they are totally dissociated in the same patient. In order to

32. Seelig: Interstate M. J. **20**:678, 1913.

33. Hammer: Folia neuro-biol. **12**:209, 1922.

elucidate the relation of Graves' syndrome to enlargement of the thymus gland, it is not necessary to theorize on any mutual activity of one organ on the other. It is sufficient merely to bring the characteristics of patients with the thymus constitution into harmony with the characteristics of patients with Graves' syndrome. This is a matter of observation entirely. It is well known that persons with the thymic constitution are extraordinarily sensitive, not only to physical influences such as traumatism, narcosis, infections, etc., but also to psychic influences. The latter is proved by the frequency of suicides and of neuroses among such patients (Kolisko,[34] Parataschew [35]). As the essential characteristic of the constitution of Graves' syndrome is the extraordinary sensitivity to physical and psychic stimuli, is it not reasonable to assume that the thymic constitution is merely a potential basis, not necessarily universal, for the development of Graves' syndrome? There are a number of facts that tend to harmonize both conditions: 1. As with Graves' syndrome, the persistent thymus is frequently a familial and hereditary condition. 2. The lymphocytosis, present in from 80 to 90 per cent of cases of Graves' syndrome and now regarded as evidence of the status thymicolymphaticus, does not disappear after thyroidectomy or after any form of treatment. The observation of Storck,[36] who found a lymphocytosis in the families of patients with Graves' syndrome, suggests a basic familial constitution as the background for the incidence of the disease, the lymphocytosis being entirely independent of thyroid influences. 3. Lymphoid hyperplasias are found with extraordinary frequency in thyroids removed from patients with Graves' syndrome. That these lymphoid deposits are not the result of inflammatory or other changes consequent on Graves' syndrome is shown by their presence in the vast majority of cases of status thymicolymphaticus, whether associated with the syndrome or not (Warthin,[17] Simmonds [37]). Hecker [38] also found such lymphatic deposits in 12 per cent of normal thyroid glands. There is evidence, therefore, that these areas of lymphatic tissue precede the incidence of Graves' syndrome and represent part of the thymicolymphatic constitution. Warthin,[17] in a publication revealing fine penetrating insight, regarded these deposits as more constant and of far greater import than the epithelial hyperplasia, and expressed the opinion that they represent the only real anatomic constitution of Graves' syndrome. Unquestionably the thymicolymphatic constitution represents the constitution in the vast

34. Kolisko: Lehrbuch der gerichtliche Medizin, Berlin and Vienna, 1902.
35. Parataschew: Virchows Arch. f. path. Anat. **273**:134, 1929.
36. Storck: Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:417, 1914.
37. Simmonds: Virchows Arch. f. path. Anat. **211**:73, 1913.
38. Hecker: Frankfurt. Ztschr. f. Path. **28**:96, 1922.

majority of cases of Graves' syndrome, but it cannot be the only one, because it has been repeatedly demonstrated that Graves' disease can occur in the absence of any evidence of the thymicolymphatic constitution. It is more consistent with established facts to assume that the basic constitution of Graves' syndrome is an entity characterized by an extraordinary sensitiveness to physical and mental influences, that in the majority of cases this sensitiveness is determined by certain anatomic peculiarities, and that in the remaining cases it is determined by environmental influences. Why a person afflicted with the thymicolymphatic constitution should show a heightened sensitivity to both physical and mental stimuli, I do not know.

The apparently inconsistent anatomic relations between the thyroid and the thymus gland and the belief that the disease was primarily glandular in origin led many investigators to the conclusion that the etiology of Graves' disease was threefold—thymogenic, thyrogenic and thyrothymogenic. Many surgeons advocated removal of the thymus gland in patients in whom thyroidectomy proved inadequate. In the light of what has already been set forth, one can readily grasp the fallacy of these conclusions, and, indeed, thymectomy for the cure of Graves' disease is now a matter only of historical interest.

Even if one admits that the neuropathic constitution is the potential of Graves' syndrome, it still remains to be explained why only a small proportion of patients with such constitutions develop the disease while others do not. There must be another factor, and this I maintain is again psychic.

EXCITING CAUSE OF GRAVES' SYNDROME

I have already called attention to the fact that when patients with the aforementioned constitution are observed shortly after periods of mental stress and emotional strain, they develop palpitation with tachycardia and trembling, and in protracted crises, even a slight swelling of the thyroid; sometimes even the eyes become more prominent. In most instances, these evidences subside when the patient calms down. Most of the observers who report on the cause of neurocirculatory asthenia during the World War, while admitting the constitutional and familial background, regard fear or emotional strain as the exciting factor (Dannehl,[39] Merklen,[40] Étienne and Richard,[41] Brooks,[7] Robey and Boas,[29] Carroll [9]). In the neurocirculatory asthenia of civil life, I have frequently noted exacerbations due to fear. Neuhof [31] reported similar observations.

39. Dannehl: Deutsche mil.-ärztl. Ztschr. **44**:44, 1915.

40. Merklen: Bull. et mém. Soc. méd. d. hôp. de Paris **41**:894, 1917.

41. Étienne and Richard: Bull. et mém. Soc. méd. d. hôp. de Paris **42**:1196, 1918.

The genesis of what may be called an attack of a mild form of Graves' syndrome is seen on a larger and more extensive scale in the development of a florid Graves' syndrome as the result of mental shocks of greater intensity. Every clinician is struck by the common clinical story that the onset of Graves' disease occurred promptly after a psychic insult or an intense emotional crisis. I have seen it occur after a robbery, a fire, a pogrom, a frightful sexual experience, a terrible confinement, an unwelcome pregnancy, the death of a close relative, the desperate illness of a child, an unrequited maternal affection, a sudden loss of possessions, the dread of an operation, an automobile accident, failure in a college examination, a hateful engagement forced on the daughter by the parents and the sudden onset of deafness.

It is notorious that there was a sudden crop of cases of Graves' syndrome in Vienna after the theater fire horror in 1882 and after the San Francisco earthquake. McCarrison [42] reported the interesting observation that in India, where endemic goiter is common, Graves' syndrome was exceedingly rare before the World War (probably because of the phlegmatic character of the natives engendered by their religions), while after the war, when the Indian soldiers returned, this disease became exceedingly common. Testimony is abundant, just as with neurocirculatory asthenia, from Marañon,[43] Étienne and Richard,[41] Merklen,[40] Railliet,[44] Kahane,[45] Rothackers,[46] Johnson,[47] Bär [48] and Dannehl,[39] that an enormous number of cases of Graves' syndrome arose as the result of fear during the World War.

It is unnecessary to quote the testimony of the host of observers who have noted the direct relation of fear to the onset of Graves' syndrome. Crile's [49] observations are especially interesting, not only because of his emphasis on fear as the inciting agent, but because of his plausible thesis that the characteristic facies and most of the symptoms of the patient with Graves' syndrome and those in man or in an animal in a state of fear are remarkably alike, and that fear is a phylogenetic attempt at flight or escape. Furthermore, realizing the important element of fear in the psychology of patients with this disease, he devised a most praiseworthy system of preoperative care in which the fear of the operation is reduced to a minimum.

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42. McCarrison, Robert: Proc. New York Path. Soc. **21**:154, 1921.
43. Marañon, G.: Ann. de méd. **9**:81, 1921.
44. Railliet: Bull. et mém. Soc. méd. d. hôp. de Paris **42**:1151, 1918.
45. Kahane: Wien. klin. Wchnschr. **28**:148, 1915.
46. Rothackers: München. med. Wchnschr. **63**:99, 1916.
47. Johnson: Lancet **2**:920, 1916.
48. Bär: Klin. Monatschr. f. Augenh. **59**:105, 1917.
49. Crile: Am. J. M. Sc. **145**:28, 1913.

In some instances (I should estimate one-fifth), a history of fear or a sudden emotional crisis cannot be obtained. Such a failure may be due to reticence on the the part of the patient or my inadequacy as a psychologist in the approach to the patient. In a few instances, a trained analyst has succeeded in obtaining such a history when I have failed. In others, however, even an exhaustive questioning has failed. In a few of these, I have obtained the impression that the Graves' syndrome arose imperceptibly from the constitutional state, i. e., formes frustes, etc., as the result of the cumulative effect of repeated mental strains of lesser degree. I witnessed one such instance in a woman who married late, and who practiced extraordinary sexual abuse.

In the residuum of 20 per cent in which a history of fear cannot be elicited, a large number give a history of the onset or reappearance of Graves' syndrome as occurring after an illness, usually an infection of the throat. This cause is also cited by observers as common. I am not entirely clear yet as to whether the actual infection is the inciting cause or the fear that the illness engenders. On deeper questioning, I have obtained the admission that during the illness there was fear of permanent invalidism or death. The illness may have been nothing more than tonsillitis, but to the sensitive victim any illness may appear serious. Fear is undoubtedly the basis of most of the many factors that have been cited as the cause of Graves' syndrome, such as pregnancy, confinement, the onset or cessation of menstruation, etc. For example, I recall instances in which Graves' syndrome was relieved by a much desired pregnancy, and one in which the syndrome, arising during pregnancy, was relieved after an easy confinement. Sattler [1] also mentioned such instances. That is why no hard and fast advice can be given to women with this constitution or with this syndrome in the matter of child-bearing. It should depend largely on their personal equation and adjustability.

In any event, the history of mental trauma is so common in Graves' syndrome that many, among whom may be mentioned Freud,[50] Stekel,[51] Oppenheim [52] and Pulay,[53] regard Graves' syndrome as a traumatic and anxiety neurosis.

RELATION OF THE THYROID GLAND TO GRAVES' SYNDROME

The administration of thyroid gland and thyroxin is poorly tolerated by patients with the Graves' constitution, because it intensifies most of the clinical manifestations with the development of mild forms of

50. Freud, quoted by Marcuse: Deutsche med. Wchnschr. **43**:70, 1917.
51. Stekel, quoted by Marcuse: Deutsche med. Wchnschr. **43**:70, 1917.
52. Oppenheim: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1923.
53. Pulay: Ztschr. f. klin. Med. **88**:87, 1919.

Graves' syndrome, such as tachycardia, tremor, some thyroid swelling and elevation of the basal metabolic rate. It is rare for exophthalmos to develop. The symptoms usually subside promptly with the withdrawal of the drug. In the phlegmatic person, it is rare to see any profound effect even after comparatively large doses.

The effects of the administration of thyroid gland to susceptible people, the almost constant association of thyroid swelling and Graves' syndrome, the alleviating effects of removal of large portions of this gland, the clinical opposition between Graves' disease and the acknowledged hypothyroidism of myxedema and, finally, the histologic evidences of epithelial hyperplasia in the vast majority of thyroid glands removed in cases of Graves' syndrome have led to the conception, prevalent since Möbius, that hyperthyroidism represents a large component of Graves' syndrome. There is no doubt that all of the evidence points that way. I do not imply that hyperthyroidism is the equivalent of Graves' syndrome. To me this syndrome represents hyperthyroidism plus constitution and perhaps other unknown factors. The problem remains, however, whether the thyroid is the primary origin of the disease and the psychic and other manifestations secondary, as many aver, or whether the thyroid manifestations are secondary and the results of other causes.

There are many reasons why the thyroid gland cannot be regarded as the primary origin of the disease. 1. It is well established that hyperthyroidism is not more common in districts where endemic goiter is prevalent, e. g., around the Great Lakes of the United States, in Switzerland and in India (McCarrison)[54]. McCarrison stated that before the World War, Graves' syndrome was extremely rare in goitrous districts, and was present only among the European residents. I shall not enter largely into the problem as to whether the distinction made by Plummer between Graves' syndrome and adenoma with hyperthyroidism is valid or not. As far as I can judge, these two diseases are the same, differing only in intensity. The same constitutions underlie both; the anatomic characters are the same, the results of thyroidectomy are alike, and the main exciting agent, fear, is a dominant factor in both conditions. Modern opinion is largely veering in this direction. 2. In clinically well recognized cases of Graves' syndrome the thyroid is often not only absent, but in about from 10 to 15 per cent no evidence of hyperplasia is present (Holzweissig,[55] Simmonds,[37] Klose and Hellwig[56]). Warthin would exclude such instances from Graves' syndrome, but this is hardly justifiable, because it would validate the argu-

54. McCarrison, Robert: The Thyroid Gland in Health and Disease, New York, William Wood & Company, 1917.

55. Holzweissig, H.: Deutsche Ztschr. f. Chir. **193**:276, 1925.

56. Klose, H., and Hellwig, A.: Arch. f. klin. Chir. **128**:175, 1924.

ment that because the majority of thyroid glands in Graves' disease show hyperplasia no case is Graves' disease unless the gland shows hyperplasia. Indeed, definitely clinical Graves' syndrome is extremely common without any thyroid hyperplasia. 3. There appears to be no parallelism between the extent and intensity of the hyperplasia and the clinical expression of the disease.

One must conclude, therefore, that despite the fact that many of the signs of Graves' disease are apparently the effects of hyperthyroidism, the gland itself is not the primary cause, and the changes that occur in the gland are the resultant factors. As the constant constitutional basis and the common excitant, fear, are of psychologic origin, these changes are probably the results of influences in the nervous system. Corroboration of this view is shown in the demonstration that the thyroid secretion is profoundly influenced by stimulation of the superior laryngeal nerve (Katzenstein,[57] Exner,[58] Wiener,[59] Ascher and Flack[60]). How far the signs of Graves' syndrome are the result of imbalance of the autonomic nervous system (Hyman and Kessel)[2] or of the peripheral or central neurons cannot, in the light of present knowledge, be determined. It is probable that the autonomic nervous system is responsible for a considerable part of the clinical expression of the disease.

The definite etiologic relationship of the psychopathic constitution and the excitant psychic insult to Graves' syndrome explains: (1) the enormous preponderance of Graves' syndrome in the female sex, (2) the rarity of this disease in childhood, i. e., before the age of puberty and (3) the comparative freedom from the syndrome of certain races, e. g., East Indians, Chinese and negroes.

Relation of Graves' Syndrome to Sex.—In Sattler's extensive statistics the proportion of females to males is 5.44 to 1. The sensitiveness and responsiveness to the environment and the more subtle emotivity of the female sex are probably in part the result of generations of protection that the male has imposed. It is not to be wondered at that the female is more sensitive to fear. In the male, I have noted that Graves' syndrome often affects those who have been single, or the favorite or spoiled child. These persons also reveal the sensitivity engendered by too great an application of protective mechanisms.

The Relation of Graves' Syndrome to Race.—There is ample testimony that Graves' syndrome is unusual in races of coarser mental fiber, in countries where the social order is simple and where the people are noted for their phlegmatic temperament. Testimony is ample that

57. Katzenstein: Arch. f. Laryngol. u. Rhinol. **5**:285, 1896.
58. Exner: Arch. f. d. ges. Physiol. **68**:100, 1897.
59. Wiener: Arch. f. exper. Path. u. Pharmacol. **61**:297, 1909.
60. Ascher and Flack: Ztschr. f. Biol. **55**:83, 1910.

Graves' syndrome is rare in India among the native population (McCarrison). Sattler found that it is also rare among the Japanese and the colored races. Up to a decade or more ago Graves' disease was considered rare in the American colored population, but as I have had the opportunity to observe, it apparently is now on the increase, probably due to the sensitization acquired through close contact with civilization among the whites and industrialization.

Graves' syndrome is very common among the Jews (Fishberg), who are notoriously a highly sensitive and emotional people, consequent to the development of keen protective mechanism engendered by generations of persecution and defensive wanderings. Marcuse [61] quoted Grotjean, who found Graves' syndrome more common in cities than in rural districts. This is as one would expect, for the strains of existence and the opportunity for psychic insult are greater in large centers of population. The incidence of Graves' disease is highest in the most civilized races and countries. This difference in incidence among races and countries depends on many other factors: the religion (whether it teaches resignation or irreconcilability in the face of vicissitudes), the social code, the character of the government, the suitability of the land for sustenance, etc. In general, those influences that tend toward conflict and the sensitization of the individual will breed Graves' syndrome. In the final analysis, therefore, Graves' syndrome is a social disease and is a product of the higher civilizations.

The Relation of Graves' Syndrome to Age.—This disease is rare before the age of puberty. In Hill's [62] series of 206 cases, only 1 occurred before that age. Of the 3,447 cases collected by Sattler, only 184 were in children below the age of 15. Hill and others expressed the belief that the common incidence of Graves' syndrome at the time of puberty corresponds to the development of the sex instinct, and there is no doubt that at this time, in girls especially, the onset of the menses is attended by considerable mental strain. But to my mind, this is not so much the reason as the fact that at this age the reasoning and emotive powers become more subtle and adjustments become more sensitive. The constitution which has hitherto been potential is now developed.

DIAGNOSIS OF GRAVES' SYNDROME

As can be gathered from all I have thus far set forth, there is no single sign or test that will make the diagnosis of this disease absolute. It can be made only by taking into consideration a host of factors. The touchstone for the diagnostic approach is the reconstruction of the patient's personality or, in other words, his constitution. Of lesser

61. Marcuse: Deutsche med. Wchnschr. **43**:70, 1917.
62. Hill, H. G.: Quart. J. Med. **22**:217, 1929.

importance, but nevertheless illuminating, is the determination of the exciting psychic insult. The insult is sometimes lacking, but as far as my experience goes, the constitution never is.

The custom has become prevalent in this country to regard the determination of the basal metabolism as the main diagnostic criterion of Graves' syndrome, especially in the differentiation of formes frustes, autonomic imbalance, etc., from the fully developed disease. For statistical purposes and as a means of offering some notion of the severity of the disease, a differentiation on the basis of a normal or heightened basal metabolism may be justified, but on a strict biologic basis such a differentiation cannot be regarded as anything but artificial. One can readily understand why this must be so when one considers that with the elevation of the basal metabolic rate, as with the elevation of a patient's temperature, there is no precise level that must be considered critical. Indeed, the basal metabolism determination in Graves' syndrome cannot be regarded of greater diagnostic value than that of clinical thermometry in febrile conditions, and the relation of Graves' syndrome to the formes frustes stage may be compared to that of the febrile and the nonfebrile period of an infectious disease. The best proof of the limitation of the basal metabolism as a diagnostic criterion of Graves' syndrome is the fact that all physicians observe cases of classic Graves' syndrome (so-called "spent" cases) without an increased basal metabolism. There is hardly any question that the basal metabolism had been elevated, but in the diagnosis one can be concerned only with data obtained at the time of observation. When the basal metabolism returns to the normal limit after thyroidectomy for Graves' syndrome, does one at the same time suddenly change the diagnosis? Most assuredly not. The basal metabolism may best be regarded not as a diagnostic sign of Graves' syndrome but as the sign of hyperthyroidism and as the best measure of activity of the disease that one possesses at present.

Others besides Warthin do not regard the clinical diagnosis of Graves' syndrome as proved unless the thyroid gland reveals the characteristic epithelial hyperplasia. Aside from the fact that, as has been shown repeatedly, no such hyperplasia has been demonstrable in certain cases of clinically classic Graves' syndrome, it is unreasonable to hold to a precise anatomic criterion when all evidence, as even Warthin admitted, shows that the pathologic thyroid is secondary and is merely a link in the chain of circumstances. It would be equally logical to say that a patient has not hypertension because anatomically the usual arteriosclerosis and nephritis were not present at autopsy, or that those diabetic patients in whom (as occasionally happens) the islands of Langerhans are found normal, did not have the disease.

THE BEARING OF THE CONSTITUTION ON TREATMENT AND RECURRENCES OF GRAVES' SYNDROME

If the relation of the constitution (autonomic imbalance, formes frustes) to Graves' syndrome is recognized, and, especially, if the fact that this constitution, whether determined by a status thymicolymphaticus or environment, is an irradicable part and parcel of the patient's personality is recognized, and, furthermore, if one acknowledges that this constitution has the potentiality to flare up under the stress of a psychic insult, one can readily understand the vicissitudes that the various methods of treatment for Graves' disease have undergone. The therapy for no disease has covered so wide a range and has undergone such rapid changes as that for Graves' syndrome. It is best to "cast the poppy of oblivion" over the host of drugs and other methods that have been tried and found wanting. I shall not enter into the modern methods of therapy, except to say that no treatment which does not take into consideration the constitution and the exciting psychic insult can be completely effective. And this is where the great difficulty enters. For, as I have shown, a study of the individual constitution involves the study not only of the personality of the patient, but of his family, his environment, his social and economic status and, above all, his mental malleability. As far as the present outlook permits one to say, each patient requires not only discerning social service, but psychotherapy. Unfortunately, social service is not yet sufficiently adequate, nor is psychotherapy whether by freudian psychoanalysis or by character building, hypnotism, behaviorism or "skilful neglect," always capable of controlling some of the environmental factors. All these psychotherapeutic methods have brought about improvement and even "cures" (more or less temporary, rarely permanent), but the number of unsuccessful cases is still large.

The estimation of the different factors that enter into the constitutional make-up is decisive in regard to whether the patient should continue with psychotherapy or should resort to surgical intervention. If the environment can be controlled, if the constitutional defect is not too deeply seated within the patient, if the Graves' syndrome is not too florid and, above all, if the patient is mentally young enough to be psychically impressionable, psychotherapy is permissible. If one cannot get at the cause, one must get at the effect, and so one comes to surgical intervention. Although the cause of appendicitis is not known "cure" can be obtained by removal of the offending organ.

Surgical intervention for Graves' syndrome is obviously based on the gross evidences of hyperthyroidism. Here the treatment has been one of rapidly changing methods, varying from ligation of the thyroid arteries to partial excision and now to almost complete excision of the

thyroid gland. There is no doubt that the results of subtotal thyroidectomy are speedier and more lasting than those obtained by strictly medical means, but one must understand that all that surgical intervention has done is to depress rapidly the basal metabolism, for the thyroid gland is responsible for 40 per cent of the bodily heat. It acts like a prolonged antipyretic in a fever. A lowered bodily metabolism must be profoundly beneficial. It is intriguing to think that part of the good results of the operation may be due to the psychic effects of the operation itself. Crile [49] discussed this aspect seriously, and concludes that psychology does not enter into the result.

Thyroidectomy, therefore, removes only the hyperthyroidism and the increase of basal metabolism; the personality of the constitution remains, a potential, given enough stimulus, to flare up into the more intense forms of Graves' syndrome. This accounts for the frequent and mysterious recurrences, no matter how thoroughly the operation was performed. As a rule, the recurrences are not usually of the severer variety of Graves' syndrome; the basal metabolism rarely reaches excessive figures, and the patients respond quickly to physical and mental rest and isolation from the environmental psychic insult. Furthermore, such recurrences may take place at any time, even years after the operation, so that reports of cures within a year or two after operation mean very little. Surgeons have been very remiss, therefore, in discharging their patients after operation without any regard to the environment to which they return; some, fortunately, realize this and give their patients instruction for the ensuing year or two. The lesson that these recurrences teach is that the treatment of the patient begins only after the operation has been performed.

SUMMARY

1. The classification of Graves' disease must be regarded from the dynamic rather than from the static point of view. In other words, it does not merely represent a disease in which various signs are artificially grouped together, but rather a biologic series of disorders that have received various names in the past. The natural history of the disease extends over a long period. The earliest phase is that heretofore known as formes frustes, "basedowoid," autonomic imbalance, etc.; the final stage is that conventionally termed Graves' disease, with the characteristic quadrad of signs—tremor, tachycardia, enlarged thyroid gland and exophthalmos. Between the primitive and the final florid form, one clinically finds various combinations of signs and symptoms. For this reason the name Graves' syndrome rather than Graves' disease is preferable.

2. The common denominator in all of these various stages is a characteristic temperament or personality which may best be termed the sensitive and emotional type. In most instances this personality precedes the onset of the syndrome and persists even after all its grosser evidences have disappeared. This sensitive and emotional personality is a large element in the constitution which predisposes to the disease.

3. This constitution is often familial and hereditary. This is evident not only in the common history of "basedowoid," autonomic imbalance, formes frustes, etc., occurring in the same family, but in the fully developed Graves' syndrome as well. A study of the family history in this disease is therefore important and illuminating. In how far this constitution is hereditary or acquired cannot be judged, but there is no doubt that it is strongly influenced by environmental factors.

4. The thymicolymphatic constitution, when it co-exists with Graves' syndrome, represents the anatomic background on which this disease is engrafted. Persons with such constitutions are sensitive not only to physical, but to psychic insult, and possess the same familial and hereditary attributes as patients with Graves' syndrome. There is no evidence that the thymus gland activates the thyroid gland or vice versa.

5. The exciting cause of the fully fledged Graves' syndrome is usually traceable to a psychic insult which is in the nature of a surprise. Such an insult ushers in the transition between the primitive stage, i. e., formes frustes, etc., and the florid form of the syndrome. In most instances the essential ingredient in this insult is fear.

6. There is every evidence that excess of thyroid function represents the predominant evidences of Graves' syndrome. All evidence, however, shows that the hyperthyroidism is secondary and not primary. The characteristic hyperplasia of the thyroid gland in Graves' syndrome is therefore sometimes lacking.

7. The greater preponderance of Graves' syndrome in the female sex is the result of the greater sensitivity of the psyche in the female.

8. The racial incidence of Graves' syndrome conforms to what one would expect of ethnologic sensitivity. It is uncommon in races of coarser mental fiber and is common in those of subtler mental reactions and where the strain of existence is keener. Graves syndrome is apparently a social disease of the higher civilizations. In the development of the influences in which the disorder is likely to develop, religion, the social and political status, the availability of the country for sustenance, etc., are probably important.

9. The relation of the psyche to the development of Graves' syndrome is shown in the rarity of this disease in children, in whom the adjustable, reasoning and emotive powers are not fully developed.

10. The determination of the basal metabolism should not be regarded so much as a diagnostic sign of Graves' syndrome as a measure of the most prominent symptom, namely, hyperthyroidism, and therefore of activity.

11. If the relation of the constitution to Graves' syndrome is recognized, it will help to explain the many failures after treatment, whether medical or surgical. This constitution persists after any form of treatment, so that cure is never wholly obtainable. The most profound effect of thyroidectomy is on the basal metabolism. Furthermore, this constitution being profoundly influenced by environment, the treatment of the patient should not cease after thyroidectomy.

THE OXYGEN AND CARBON DIOXIDE CONTENT OF BLOOD FROM THE INTERNAL JUGULAR AND OTHER VEINS *

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A principal function of the blood is that of respiration, giving oxygen to the tissues and receiving carbon dioxide. The difference in the gaseous content of arterial and venous blood is a measure of the metabolic activity of the tissues or of the speed of the blood flow through them, or of both. To what extent do the various portions of the body vary in their utilization of oxygen? Is the blood taken from a superficial vein of the arm essentially the same in its gaseous composition as blood taken from other accessible veins?

The only observations bearing on this subject that we have seen are those made during certain experiments on animals by Uyeno and Dor.[1] They gave values for the oxygen saturation of the blood (as determined by the Barcroft differential apparatus) in various veins in six experiments. These values varied widely.

In order to answer the questions outlined for the human subject, we have measured the oxygen and carbon dioxide content of blood from various blood vessels, viz., the brachial, radial or femoral artery, the internal and external jugular, the femoral and the basilic veins.

METHODS AND MATERIAL

In order that the results should be as dependable as possible, certain precautions were observed. The subjects were required to lie quietly for half an hour before the blood was taken. This was drawn without the aid of a tourniquet, with the vein at the level of the heart. The room temperature was kept constant. Care was taken to avoid pain on puncture by preliminary local anesthetization of the skin. For puncturing the internal jugular vein we used the technic described by Myerson and his associates.[2] We first carefully anesthetized the tissues to be traversed by means of 1 or 2 cc. of a 1 per cent solution of procaine hydro-

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1. Uyeno, K., and Dor, Y.: Studies on the Respiration and Circulation in the Cat: II. The Oxygen in the Venous Blood, J. Physiol. **57**:14 (Dec.) 1922.

2. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

chloride, introduced through a 1½ inch 26 gage needle. For drawing the required 10 cc. of blood, a 1½ inch 20 gage needle was used. If the patient did not remain relaxed or if he experienced undue pain, the attempt to obtain blood from the internal jugular vein was abandoned. It was not feasible to withdraw blood from the various loci simultaneously. Also it was thought that such a concerted attack would unnecessarily excite the subject, thus complicating the results. We therefore drew blood from the veins in sequence, varying the order in different patients. In some of the subjects used it was found that there was considerable variation in the gaseous content of blood drawn at intervals from the same vein. For this reason we believe that comparison of individual measurements is not of as much value as comparison of average values obtained from a fairly large group. Blood was taken under oil, and analysis was begun at once. The portable constant volume apparatus of Van Slyke [3] was used.

None of the subjects had any serious cardiac or pulmonary lesion. All were patients in the neurologic service of the Boston City Hospital. Most of them were subject to epilepsy. A few were used more than once.

The following observations present data, a portion of which has already appeared in abstract form.[4]

TABLE 1.—*Average Measurements of Blood Gases from Various Vessels*

	Artery				Internal Jugular Vein				Cubital Vein				External Jugular Vein				Femoral Vein			
	Oxygen				Oxygen				Oxygen				Oxygen				Oxygen			
Number of Observations	Content	Capacity	Percentage Saturation	CO_2 Content	Content	Capacity	Percentage Saturation	CO_2 Content	Content	Capacity	Percentage Saturation	CO_2 Content	Content	Capacity	Percentage Saturation	CO_2 Content	Content	Capacity	Percentage Saturation	CO_2 Content
14	18.5	20.5	90	49.6	12.4	19.8	62	56.2	14.0	19.6	71	53.8	16.8	20.3	83	51.6	14.0	20.1	70	53.3
40	19.2	20.5	94	49.5	12.4	19.9	62	55.8	13.6	19.8	69	53.8	17.8	20.5	87	51.2				
51	18.6	20.1	92	49.2	12.1	19.1	63	55.2	13.6	19.4	70	53.4								
60	....	....	..	....	12.6	19.9	63	54.9	13.5	19.8	68	53.2								

RESULTS

The average results obtained are shown in table 1. In fourteen subjects, blood was secured from five vessels. Average values in these instances for the percentage saturation of the blood with oxygen and its carbon dioxide content are shown graphically in chart 1. It will be seen that the values for venous blood obtained from a cubital and from a femoral vein were essentially the same. The surprising contrast was in the blood from the two jugular veins. That from the external jugular approached the composition of arterial blood, whereas that from the internal jugular was more "venous" than blood from the arm.

These results were so unexpected that a much larger series of observations was made in which blood was drawn from four vessels. The

3. Van Slyke, D. D.: Portable Form of Manometric Gas Apparatus and Certain Points in Technique of Its Use, J. Biol. Chem. **73**:121 (May) 1927.

4. Lennox, W. G.: Observations Concerning Intracranial Circulation in the Human Subject, J. Clin. Investigation **7**:517 (Aug.) 1929.

average results obtained in forty experiments are shown in table 1 and in the left hand portion of chart 2. In this larger group the composition of the arterial blood was more nearly normal than in the smaller group. (Many of the epileptic subjects used had a low oxygen saturation of the arterial blood, a matter that will be presented elsewhere.) The gaseous content of the external jugular blood bore about the same relation to that of the arterial blood as in the smaller group. The difference between blood from the internal jugular and

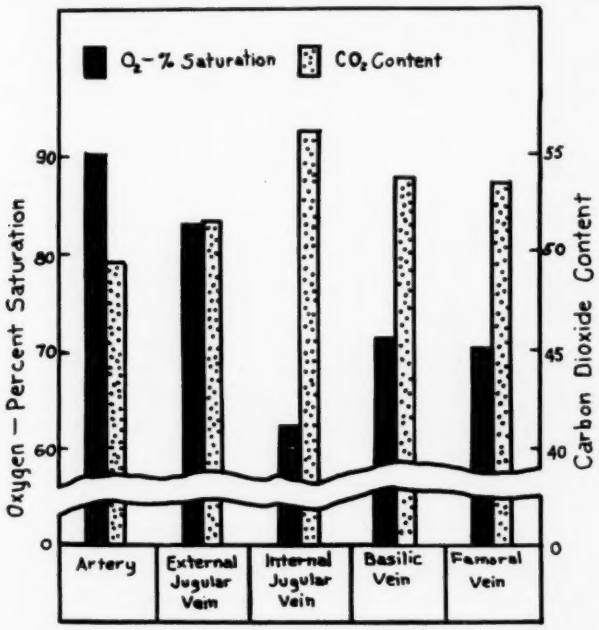

Chart 1.—Average results concerning the percentage saturation with oxygen (solid columns) and the carbon dioxide content (dotted columns) of the blood in fourteen patients, the blood being drawn from an artery and the external jugular, internal jugular, basilic and femoral veins. The percentage saturation with oxygen is given in the left hand ordinate and the carbon dioxide content in the right hand ordinate.

from the cubital veins was very nearly as great. In a still larger series of sixty observations, blood was obtained from only two veins, the internal jugular and a vein of the elbow. Here, as in the smaller groups, blood from the internal jugular vein was more nearly reduced than blood from a superficial vein of the arm. Results are shown in table 1 and in the right hand portion of chart 2.

There were great individual variations in the relationship of the blood from the internal jugular vein to that from the veins of the arms. In some persons blood from the internal jugular vein had the higher percentage saturation with oxygen, and in many patients blood from the two sources was practically the same. From patient to patient and from time to time the gaseous content of blood from the internal jugular was more constant than that from the cubital vein. We are endeavoring to determine factors which influence the differences observed.

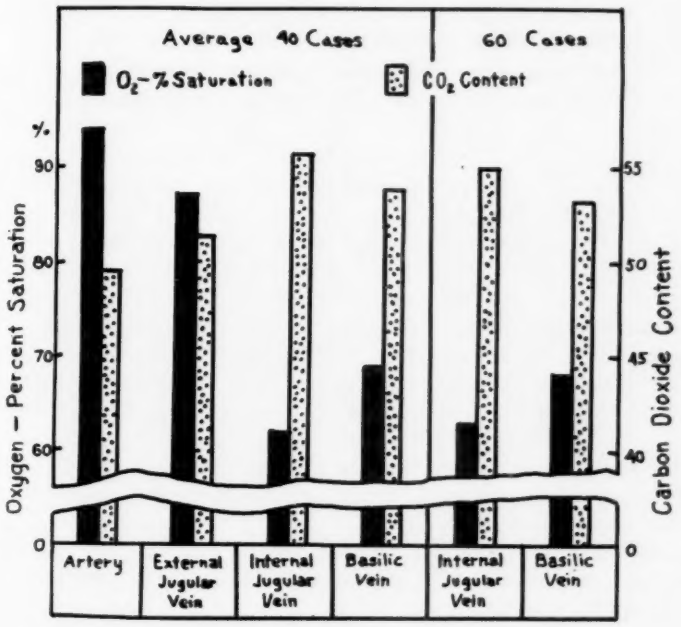

Chart 2.—The left hand portion of the chart gives the average results in forty cases, and the right hand portion the average results in sixty cases. The columns and the ordinates are the same as in chart 1.

We were not surprised to find that blood from the external jugular vein is nearly arterial. The tissues of the face and scalp are richly supplied with vessels. The metabolic rate of the skin and subcutaneous tissue is presumably low. One wonders to what extent the overabundant blood supply of the face with the resulting "complexion" may be the result of natural selection. Another factor may be the need of keeping an exposed surface of the skin warm. Blood from the veins on the back

of the hand is also but little reduced.[5] It would be of interest to know whether the blood which drains the face and scalp in animals is so nearly arterial.

We were not prepared to find such a low oxygen content of blood in the internal jugular veins. One might suppose that the brain, above all other tissues, would be so abundantly supplied with oxygen that blood leaving the cranium would carry a large unused amount. The relatively low oxygen saturation of blood in the internal jugular vein means either an unusually high rate of oxygen consumption in the brain or a slow rate of blood flow, or both. Observations that we are making should throw some light on the relative importance of these two factors. The difference in oxygen content of blood entering and leaving the brain in our patients (6.5 per cent by volume) was almost the same as the difference reported for rabbits (6.9 per cent by volume).[6]

THE RESPIRATORY QUOTIENT

Doisy and Beckmann[7] pointed out that for a portion of the body a value for the respiratory quotient can be arrived at by dividing the increase in the carbon dioxide content of the venous blood by the decrease in its oxygen content, with reference to the carbon dioxide and oxygen content of arterial blood. Himwich and Castle[8] corrected the formula to allow for any change in the concentration of the blood that might occur in its passage through the tissues. For a group of anesthetized dogs, they obtained an average respiratory quotient of 0.71 for isolated muscles deprived of skin and subcutaneous tissues, and a quotient of 0.77 for the intact leg.

Individual measurements are not of value because of alterations in the carbon dioxide content of blood associated with changes in breathing, in acid base relations or in the rate of diffusion of oxygen and carbon dioxide through the skin. We calculated the respiratory quotients for the average measurements obtained in our patients, correcting the quotients for changes in concentration of the blood. In a series of fifty-one observations, the average respiratory quotient for blood from the arm was 0.84, for blood from the brain, 0.9 and (in a smaller

5. Goldschmidt, S., and Light, A. B.: Method of Obtaining from Veins Blood Similar to Arterial Blood in Gaseous Content, J. Biol. Chem. **64**:53 (May) 1925.

6. Yamakita, M.: The Relation of the Blood Flow to the Gaseous Metabolism of the Brain, Tohoku J. Exper. Med. **3**:556 (Dec.) 1922.

7. Doisy, E. A., and Beckmann, J. W.: The Relations Existing Between Arterial and Venous Blood of the Dog with Special Reference to the Plasma Chlorides, J. Biol. Chem. **54**:683 (Dec.) 1922.

8. Himwich, H. E., and Castle, W. B.: Studies in the Metabolism of Muscle: I. The Respiratory Quotient of Resting Muscle, Am. J. Physiol. **83**:92 (Dec.) 1927.

series of forty cases) for blood from the face, 1.2. Judging from Himwich and Castle's observations, skin and subcutaneous tissue would seem to have a comparatively high quotient. The fact that the superficial veins at the elbow derive their blood in large degree from skin and subcutaneous tissue might account for quotients somewhat more elevated than those of Himwich and Castle, in whose experiments blood was obtained from the femoral vein. The external jugular vein likewise drains a skin area. It is doubtful, however, whether significance can be given to this very high quotient, because blood from the external jugular vein differed so little from arterial blood. The respiratory quotient of 0.9 for the brain may be compared with a value of 0.86 determined by Loebel [9] by means of the apparatus of Warburg for the gray matter of the brains of two rats, and with a value of 1 for anesthetized dogs by Himwich and Nahum.[10]

The chief interest, however, lies not in the absolute values obtained, but in a comparison of the quotients for the arm and the brain. In Himwich and Castle's experiments, muscle seemed to have a quotient

TABLE 2.—*The Average Oxygen Saturation and the Average Sugar Content of Blood from Various Vessels, in Twenty-Five Cases*

Source of Blood	Percentage Saturation With Oxygen	Sugar Content, Mg. per 100 Cc.
Artery	94	96.4
External jugular vein	87	94.4
Cubital vein	67	93.2
Internal jugular vein	62	88.7

lower than skin and muscle; in our observations, the brain had a higher quotient than the arm. This higher quotient suggests a relatively higher consumption of carbohydrate in the metabolism of the brain. This suggestion makes observations with regard to blood sugar of interest. Myerson and Halloran,[11] in a large group of psychotic patients, found that values for sugar in the blood tend to be lower for the internal jugular than for the cubital vein. In twenty-five experiments, we measured blood sugar as well as blood gases. The average results are shown in table 2. The average decrease of sugar in venous, as compared with arterial, blood was 7.7 mg. per hundred cubic centimeters for blood from the internal jugular vein, 3.2 mg. for blood from a superficial vein of the arm and 2 mg. for blood from the

9. Loebel, R. O.: Beitrag zur Atmung und Glykolyse tierischer Gewebe, Biochem. Ztschr. **161**:219, 1925.

10. Himwich, H. E., and Nahum, L. H.: Respiratory Quotient of the Brain, Proc. Soc. Exper. Biol. & Med. **26**:496, 1929. More extensive observations will be published elsewhere.

11. Myerson and Halloran: Personal communication to the authors.

external jugular vein. In single observations the difference of 4.5 mg. (about 5 per cent) in the blood coming from the arm and that coming from the brain would be of no significance, but as an average value, representing a fairly consistent individual difference, we believe that it is of significance. It is possible, of course, that the increased consumption of sugar is related to a decreased rate of blood flow through the tissues. This idea finds some support in the fact that the bloods which were low in sugar were also low as regards their saturation of oxygen. On the other hand, the sugar content of the internal jugular blood, in comparison with its oxygen saturation was disproportionately low. Because in making these observations we are not able to measure the blood flow or the metabolic rate of the brain, we cannot say that the observed increase in the respiratory quotient was accounted for by the observed increase in consumption of sugar. The observations indicate merely that both the respiratory quotient and the sugar consumption of the brain are a trifle higher than those of the superficial tissues of the arm.

SUMMARY

In a large series of patients, we measured the oxygen and the carbon dioxide content of the blood from an artery and from various veins. The gaseous content of blood from the femoral vein was found to be the same as that of blood from a cubital vein. In sharp contrast, blood from the internal jugular vein was more reduced and blood from the external jugular less reduced than from a cubital vein. These statements are true for average values. Measurements for individual patients varied widely.

In a series of fifty-one patients, the average corrected respiratory quotient for blood from a cubital vein was 0.84 and from the internal jugular vein, 0.9. More sugar disappeared from the blood in its passage through the brain than in its passage through the arm. The former of these observations suggests that in the metabolism of the human brain, carbohydrates are unusually important.

PULMONARY TUBERCULOSIS

TREATMENT IN ALLERGEN-PROOF CHAMBERS *

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Seven years ago I suggested the theory that the undeniable influence that high altitude exercises on asthma and other allergic diseases is due to the absence of climate allergens in these regions. The correctness of this idea was proved by the demonstration of the fact that the effect that high altitude has on these diseases may be obtained in low-lying districts and in moist climates simply by technical methods, which involve the construction of a so-called allergen-proof chamber in the house of the patient. We have shown that "climate" in relation to allergic diseases is for the most part related to the condition of the soil, and that a moist soil with high absorbing power for water and a high level of ground water is unfavorable for patients with asthma, whereas a dry soil (sand, rock, chalk) with a low water capacity and a low level of ground water is favorable. Moreover, it was shown that the moist soil exerts its bad influence for the most part by favoring the conditions for the growth of micro-organisms in the house, i. e., in carpets, rugs, furniture, floors and walls and probably also under the floors. The climate allergens formed outside of the house are less active.

These considerations led to the conclusion that the sufferer from climate allergy may be brought into an almost normal condition by protection against the allergens prevailing in the air in his own house. This condition may be realized by the building of a small chamber in the bedroom of the patient, constructed of an asbestos material (eternite), which prevents the growth of micro-organisms. The simple type of these chambers is ventilated with air from a height of 30 feet (9.1 meters) above the roof of the house or even from outside a window blown into the chamber through metal pipes by means of a ventilator. The air is heated before it enters the chamber. In some cases the outside air has to be purified, which is done by cooling so that it loses the greater part of its water; this process of condensation removes the impurities from the air.

My co-workers and I have used this method of treatment in more than 1,000 cases of asthma, and we have found that exactly the same percentage of patients who are benefited by residence in high altitude

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are also relieved from allergic attacks in the allergen-proof chamber. Of course this relief lasts only as long as the patient breathes air that is free from allergens, just as the influence of high altitude ceases as soon as the patient goes back to low-lying districts. It has been proved, however, that the principle of the allergen-proof chamber may also be used for effecting permanent relief by the construction of allergen-proof chambers in the private house of the patient. Our results with this method have been published more extensively elsewhere.

During our work on the treatment for allergic diseases with allergen-proof chambers, we realized that the principle of this treatment might be extended to other diseases, and the first other disease to be studied was pulmonary tuberculosis. Our attention had been drawn to this disease by the circumstance that some patients with asthma combined with tuberculosis applied for admittance to our clinic, and did extremely well. They were relieved not only of their asthmatic attacks, but also of their pulmonary tuberculosis in a relatively short time. These cases, although not large in number, were the more impressive since the patients had been treated before in sanatoriums with little success in our low altitude. These observations brought us to the realization that the beneficial influence of high altitude in such cases of asthma combined with tuberculosis would have to be ascribed to the lack of climatic allergens in air at a high altitude. Then we were confronted with this problem: Why does high altitude cause improvement in cases of pulmonary tuberculosis uncomplicated with asthma? A brief survey of literature on the subject did not give satisfactory information. Neither lack of oxygen nor irradiation with ultraviolet light nor dryness of the air seemed adequate therapeutic factors, and we concluded that probably purity of the air—a factor repeatedly suggested by various authors but never generally accepted—would prove to be the most important therapeutic agent of high altitude; we included in this conception the supposition that in this case purity of air would mean lack of climatic allergens.

Since we had at our disposal a clinic with allergen-proof chambers and facilities for the ventilation of these chambers, either with outside air or with air purified by cooling, we could easily put our theory to an experimental test. Researches along this line have now been performed in our clinic for more than three years, and the results have entirely convinced us of the correctness of our theory.

In judging these results, our cases of pulmonary tuberculosis uncomplicated with asthma may be divided into three groups.

The first group contains light cases with apical or subapical catarrh, a temperature below 38 C. (100.4 F.), a pulse rate below 100, little sputum or no sputum at all, and if sputum is present, an absence of tubercle bacilli. It is known that such cases as a rule clear up quickly,

if rest, good food and good air are obtained; high altitude gives excellent results in these cases. Our experience with this group was, without exception, good. Residence in the allergen-proof chamber with purified air resulted in a quick disappearance of local and general symptoms. This disappearance of symptoms sometimes was realized in such a short time that I strongly doubt if all of these cases—although for the most part they were sent to us by competent specialists, who could support their diagnosis with roentgen examination—may be considered as cases of true tuberculosis. I incline to the view that a number of these patients suffered from a disease due to humid climate, i. e., hypersensitiveness to climatic allergens, which in these cases do not produce the ordinary symptoms of asthma or vasomotor rhinitis, but "low fever," coughing, râles in the apex of one or both lungs and signs of induration or cicatrization in the roentgenogram. As has already been noted, these cases clear up quickly in the allergen-proof chamber. In the absence of tubercle bacilli the absolute proof of the origin of the disease often cannot be given, and I doubt whether it is wise to bring those patients to a sanatorium that houses cases of open tuberculosis, on account of the risk of infection.

The patients described are sometimes "cured" after residence in the clinic. Sometimes, however, the symptoms reappear after the patient returns to his former surroundings. In such cases, the condition of the patient's home will have to be changed, as was fully described in my paper on social work in the treatment for asthma.

Examples of cases belonging to the first group follow:

CASE 1.—S. Z., a girl, aged 10 years, remained subfebrile after recovery from scarlatina; she coughed and showed signs of catarrh of the apex of the right lung. A specialist diagnosed the condition tuberculosis and considered the patient dangerous for her brothers and sisters. The Pirquet reaction was positive. On admission to the clinic the patient had râles at the apex, considerable coughing, and a maximum rectal temperature of 37.5 C. (99.5 F.). After residence in the allergen-proof chamber for ten days, she had a temperature of 37 C. (98.6 F.), she did not cough, and she had no pathologic signs on percussion or auscultation; she left the clinic after two months, completely recovered.

CASE 2.—Tr., a girl, aged 11 years, had a condition almost identical with that in case 1. She stayed in the clinic for six weeks and left completely recovered. This was probably a case of climatic allergy without tuberculosis.

CASE 3.—Cha., a woman, aged 22, had bronchitis and hemoptysis three years before admission to the clinic. She also suffered from hay-fever. She rested at home for three months, then spent six months in a tuberculosis sanatorium and, later one year in same sanatorium. No improvement occurred. She was sent to our clinic with a diagnosis of pulmonary tuberculosis of the apex of the left lung.

On admission, she had râles at the apex of the left lung, the sputum was negative for tubercle bacilli, and the maximum temperature was 37.9 C.

(100.2 F.). Shortly after admission she had an attack of influenza; five weeks after admission her temperature was normal, and she had no sputum nor râles. Sedimentation time was normal. After four months she left the clinic without any pathologic sign. She applied at another hospital for a position as nurse and was accepted.

Case 4.—Gr., a man, aged 26, was treated for pulmonary tuberculosis in a sanatorium for more than a year without showing any improvement. He had suffered from asthma. On admission to our clinic he weighed 85 Kg. (187 pounds), but felt weak; the temperature varied between 36.5 and 37.7 C. (99.8 F.); on the right side of the thorax, moist râles were heard at the apex, and also in the axillary line and under the scapula; the sputum amounted to 20 to 40 cc. daily, and contained tubercle bacilli.

Treatment in the clinic caused improvement in breathing after one or two weeks. The amount of sputum diminished after three weeks; from that time no more tubercle bacilli were found. After three months the temperature was normal, there was no sputum or râles, and the patient was allowed to be out of bed for four hours; he went outdoors for one hour daily.

He then suffered from influenza, with a high temperature, an increased amount of sputum, moist râles, but no tubercle bacilli. Recovery was slow, but several months after admission to the clinic he left in perfect condition, with a normal temperature and raising no sputum; the moist râles had disappeared. He was completely fit to take up his work again. The sedimentation time was 17; it had been as high as 29 three months previously.

The second group of patients with tuberculosis contains relatively light cases, and the third group the severe cases. For the sake of convenience, the last group will be considered first.

In the acute forms of this group we see caseous pneumonia and in the chronic forms large cavities, sometimes accompanied or followed by caseous pneumonia. A high temperature, a high pulse rate and large masses of sputum with large quantities of tubercle bacilli are generally found here. The allergen-proof chamber cannot cure these patients. Such cases are not cleared up by residence in high altitude; indeed, high mountain air may even be noxious to the patients, so that they are not even admitted to sanatoriums in high altitudes.

It may be remarked, however, that in these cases the allergen-proof chamber has one special advantage above sanatoriums in high altitudes. Sanatoriums situated at a height of about 3,000 to 4,000 feet may, in severe cases of pulmonary tuberculosis, do harm to the patient; the allergen-proof chamber can never do any harm. We have observed some patients who could not stand the very dry air that is often used to ventilate the chamber. This disadvantage may be eliminated by a single manipulation which turns a valve in our ventilation system and offers simple outside air to the patients. Moreover, the dry air may easily be moistened.

The fact that, unlike high altitude, the allergen-proof chamber can never do any harm enables one to try the effect of residence in this chamber in almost every case of pulmonary tuberculosis, so that the

line drawn between the second and the third group need not be very sharp, and many patients who could not risk a trip to a high altitude might be allowed a trial in the allergen-proof chamber. Consequently, the number of patients who may be given a chance of cure is enlarged.

The most important group of patients with tuberculosis, from the therapeutic point of view, consists of those who suffer from open tuberculosis of the lungs, with symptoms of bronchitis or small cavities, a temperature up to 38 C., a pulse rate up to about 100, a fair amount of sputum containing tubercle bacilli and tuberculous lesions that may be clearly demonstrated by roentgen physical examination, but who still offer fair possibilities of a cure.

Almost all of these patients show definite subjective and objective signs of improvement during the first weeks or months after admission, and it is our experience that if improvement occurs at all, it starts within the first three or four weeks. Patients who have not shown definite improvement after two months are considered by us as inapproprite for treatment in the allergen-proof chamber, and are advised to go home.

In cases that show improvement, the first salutary symptom, as a rule, is diminution of coughing and more ease in breathing. This form of improvement is often experienced by the patient during the first two or three days, and we have learned to consider this a good omen. Along with the improvement in breathing and relief from coughing the temperature and pulse rate may become lower; usually this occurs after three or four weeks; simultaneously the quantity of sputum may or may not decrease. As a rule, the body weight increases considerably, and the general condition of the patient improves.

As has been mentioned, we observe this initial improvement in the patient's condition in most of the cases of this group, sometimes even in patients whose condition has to be considered as incurable, and who ultimately die in the clinic.

The initial improvement may continue and lead to a definite improvement or to a cure of the patient, or it may come to a standstill. In the last instance we have at least obtained a temporary relief, reduced the suffering of the patient considerably and probably lengthened his life. Most of these patients remain on this level till an acute intermittent infection, often an attack of influenza or "cold" throws the balance to the unfavorable side.

It should be remembered that all the observations mentioned are related to treatment in the allergen-proof chamber only, all other therapeutic measures, including excessive feeding, being excluded during the first two months of observation; drugs are given only when the patient has been accustomed to take them, and even then we try to reduce the amount as soon as possible. Active therapy is never started before the observation of the patient has been finished.

Examples of some cases of the second group of pulmonary tuberculosis uncomplicated with asthma follow.

CASE 5.—Gr., a woman, aged 21, had been treated at home for six months for pulmonary tuberculosis; the condition was regressive. On her admission to the clinic, extensive tuberculous bronchitis was found on both sides; she had moist râles over the entire right side, a maximum temperature of 38.2 C. (100.7 F.), and sputum amounting to about 100 to 150 cc. daily which was positive for tubercle bacilli; her weight was 55 Kg. (121.2 pounds). After fourteen days' residence in the allergen-proof chamber, she showed marked improvement; after five weeks, her temperature was generally 37.3 C. (99.1 F.), rising only occasionally to 37.5 C. Sputum amounted to 60 cc. and was positive for tubercle bacilli. The patient weighed 56.5 Kg. (124.5 pounds). Three months after admission she had a temperature of 37.3 C. and from 35 to 50 cc. of sputum showing no tubercle bacilli; the condition in the chest had cleared up considerably, and the patient weighed 60 Kg. (132.2 pounds).

One year after admission the patient left the clinic feeling completely well and able to do her work; her temperature had been normal for many months. Sputum amounted to 30 cc. and was negative for tubercle bacilli; except for a small cavity on the right side, there were no pathologic signs in the lungs.

CASE 6.—Wi., a woman aged 23, had suffered from tuberculosis for about two months before admission to the clinic. Her brother had been treated for tuberculosis in our clinic with complete success. Tuberculosis of the apex of the left lung was found and the sputum was positive for tubercule bacilli; the temperature was normal. There were moist râles in the apex of the left lung and dry râles in the apex of the right.

In the allergen-proof chamber she showed rapid improvement. After three weeks there was no coughing or sputum, the moist râles had disappeared, and dry râles were heard only occasionally. Six months after admission she was completely well. After leaving the clinic, she resumed her profession as teacher.

Although nobody doubts that residence in high mountain air has a beneficial influence in many cases of pulmonary tuberculosis, every one will admit that high mountain air does not bring the ultimate solution of the problem of tuberculosis. But there is also no doubt about the fact that the campaign against tuberculosis would be much more effective if high mountain air could be available for all patients with pulmonary tuberculosis who might be benefited by it. This, of course, will never be attainable, and it is for that reason that I emphasize the importance of the fact that by relatively simple and not too expensive technical methods everything that high mountain air might offer for the improvement of the tuberculous patient may be obtained in any place and in any climate. The advantage of the new method does not stop here. High mountain air is wonderful in certain periods of the year, but may be very cold and moist and distinctly disagreeable during other periods; moreover, in certain cases of pulmonary tuberculosis it may actually do harm to the patient. All those disadvantages are eliminated by the "artificial high mountain air" which the allergen-proof chamber offers. Conditions with reference to temperature, humidity and purity of the air may be kept constant for weeks and months.

The accompanying chart gives the course of the relative humidity during a period of five days in one of our allergen-proof chambers, ventilated with cooled air. On the left side of the curve is shown the relative humidity in one of the other rooms of the clinic not ventilated by special arrangement, so as to show the great difference in humidity between an ordinary room and an allergen-proof chamber.

In cases of asthma, residence in allergen-free air is helpful only as long as the patient is kept in these allergen-free surroundings. In pulmonary tuberculosis, however, a real cure may be effected by residence in the allergen-proof chamber for several months or a year. After this period it is still preferable for the patient to live in conditions which resemble those of the allergen-proof chamber as far as possible. This may be achieved either by the construction of an allergen-free chamber in the house of the patient or by changes in the patient's bedroom and other

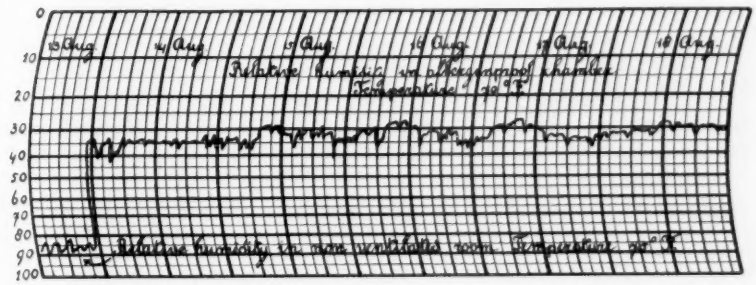

Chart showing the relative humidity in an allergen-proof chamber for five days. The small portion of the curve at the left indicates the relative humidity in another room of the clinic not ventilated by special arrangement.

rooms of the house. Both matters have been discussed by me in other papers.

The installation of an allergen-proof chamber in private houses has hitherto been seriously handicapped by the circumstances that: (1) the installation was rather expensive, and (2) the installation could be moved from one house to another only with difficulty and at considerable cost. Both difficulties have been met by the German constructor of the chambers, who found a device by which the chamber can be easily moved and placed in any room; moreover, he reduced the price considerably. In this way the allergen-proof chamber in the future will not only be a necessary addition to any clinic in which patients with diseases of the lungs or bronchi are treated, but will also become an important help in the treatment of patients at home, and thus become an instrument, not only of interest for the physician who works in clinics or sanatoriums, but also for the general practitioner.

THE SPECIFIC EFFECT OF BILE SALTS ON PNEUMOCOCCI AND ON PNEUMOCOCCUS PNEUMONIA *

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In 1900, Neufeld [1] discovered that pneumococci in suspension were dissolved by adding bile to them.

Since that time, others have shown that solutions of the bile salts, i. e., sodium glycocholate and sodium taurocholate acted in the same way, and that whole bile was not necessary. In fact, there is evidence that the cholate part of the molecule is really the active part causing the lysis. This is one of the classic tests for the identification of pneumococci.

It is interesting to watch Neufeld's phenomenon under the high power of the microscope. To obtain this, mix a drop of pneumococcus suspension and a drop of bile salt solution on a glass slide, placing a cover-slip glass on it. The pneumococci gradually dissolve, becoming smaller and smaller. They pass through the stage in which they exhibit the brownian movement, and finally disappear.

Bile-solubility was found by Schilling [2] and Neufeld [1] to be a characteristic of trypanosomes and spirilla as well as of pneumococci. Knowing the specific action of quinine on spirilla and trypanosomes, certain workers were led to try quinine and some of its derivatives in the treatment for pneumonia. Along this line of reasoning, ethylhydrocuprein was developed.

Since pneumococci are soluble in solutions of bile salts, my co-workers and I thought of using the bile salts themselves in the treatment for pneumonia. This paper deals with the treatment for pneumonia by the bile salts, sodium taurocholate and sodium glycocholate, with some laboratory experiments on the salts and their properties.

EXPERIMENTAL WORK

In our work we found that suspensions of pneumococci are lysed by sodium taurocholate (Merck) in extremely dilute solutions. (This product, called sodium taurocholate 50 per cent by the manufacturer, is stated to run between 45 and 55

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* From the U. S. Veterans' Hospital.

1. Neufeld: Ztschr. f. Hyg. u. Infektionskrankh. **34**:454, 1900; Arb. a. d. k. Gsndhtsamte. **25**:494, 1907.

2. Schilling: Centralbl. f. Bakteriol. **31**:452, 1902.

per cent, the balance being chiefly the glycocholate with small amounts of the other bile salts. This is the product that was used in the following work and is what is meant when the term "bile salts" is used.) For a solvent we consistently used an 0.85 per cent solution of sodium chloride. We added serial dilutions (from 1:20 to 1:25,000) of sodium taurocholate to suspensions of pneumococci. Appropriate controls were made with salt solution. It was found that lysis does not depend on the concentration of the bile salts, Neufeld's phenomenon being present in the most dilute solution used. For prompt lysis the higher concentrations are needed. For the dilute solutions the readings were made at intervals, the tubes being kept in an incubator and shaken before reading. The most

TABLE 1.—*Lysis of Pneumococci by Bile Salts* *

Solution	Result
50:1,000 (5.0%)	Prompt clearing
20:1,000 (2.0%)	Cleared within 10 minutes
10:1,000 (1.0%)	Cleared within 10 minutes
8:1,000	Cleared within 30 minutes
6:1,000	Cleared within 30 minutes
4:1,000	Cleared within 30 minutes
2:1,000	Cleared within 30 minutes
16:10,000	Clearer within one hour
12:10,000	Clearer within one hour
8:10,000	Clearer within one hour
4:10,000	Clearer within one hour
2:10,000	Clearer within one hour
16:100,000	Clearer within two hours
12:100,000	Clearer within two hours
8:100,000	Clearer within two hours
4:100,000	Clearer within two hours

* The controls remained cloudy

TABLE 2.—*Lysis of Pneumococci in Tubes Containing Serum*

Pneumococci Suspension, Cc.	Plus Type Serum, Cc.	Precipitate	Plus Bile Salts, Cc.	Plus Bile Salts, %	Result
0.5	0.5 1:5	No	0.5	10	Cleared
0.5	0.5 1:10	No	0.5	10	Cleared
0.5	0.5 1:20	No	0.5	10	Cleared
0.5	0.5	No	0.5	sodium chloride	Cloudy
0.5	0.5 (specific)	Yes	0.5	10	Unchanged
0.5	0.5 sodium chloride	No	0.5	10	Cleared

dilute solutions showed clearing when compared with controls, but did not become completely clear. This was interpreted as being due, not to the dilute solution, but to the small actual mass of bile salts available as compared with the number of organisms. The results of these tests are shown in table 1.

After determination of the type of pneumococci with specific serums, there were always a number of tubes in which agglutination, of course, did not take place. To these tubes were added solutions of biles salts, and lysis took place just as in the controls without serums. If bile salts were added to tubes in which agglutination had occurred, the clumps did not dissolve. These results are shown in table 2. It is interesting that the action of agglutinins on pneumococci makes them nonsoluble in bile salt solutions.

It is seen from the experiments represented in table 2 that serum does not prevent lysis of pneumococci by bile salts. Another group of experiments along this line was performed with human serum. These results are expressed in

table 3. Bile salts were added to human serum in a 10 per cent solution. To this "bile-serum," as it was called, we added equal parts of pneumococci suspension. This reduced the concentration of the sodium taurocholate to 5 per cent. We found that prompt lysis did not take place, but that there was sufficient clearing after an hour to detect lysis. After about eight hours the tubes were as clear as the controls. Controls were made with equal parts of "bile-serum" and 0.85 per cent sodium chloride. Controls by contrast were obtained by repeating the experiment and comparing the freshly prepared tubes with those of eight hours previously. In performing this experiment it is desirable to employ serums that do not contain agglutinins for pneumococci. Although interference with lysis did take place, the serum did not prevent lysis but merely delayed it, so that readings in these experiments had to be made up to twelve hours. It was found that Neufeld's phenomenon takes place slowy in the presence of serum.

TABLE 3.—*Neufeld's Phenomenon in the Presence of Human Serum* *

Solution	15 Min.	1 Hr.	2 to 8 Hrs.	10 Hrs.
0.5 cc. bile-serum 10% plus 0.5 cc. Pneumococcus Suspension	Cloudy	Clearer	Clearer	Clear as control 1

Control 1 was obtained with 0.5 cc. of bile-serum plus 0.5 cc. of 0.85 per cent sodium chloride; control 2 with 0.5 cc. of bile-serum plus 0.5 cc. of pneumococcus suspension prepared at the time of comparison; this is the more obvious control by contrast. Bile-serum consisted of 10 per cent bile salts in human serum. The final concentration of bile salts was 5 per cent.

TABLE 4.—*Effect of Bile Salts on the Antibody Action of Specific Serums on Pneumococci*

	Bile Salts 10 per Cent in Homologous Serums, 0.5 Cc.	Bile Salt 10 per Cent in Indifferent Serums, 0.5 Cc.	Homologous Serums, 0.5 Cc.	Indifferent Serums, 0.5 Cc.
Pneumococci suspension, 0.5 cc.....	Agglutination	Cleared	Agglutination	Cloudy
Supernatent fluid from, pneumococci, 0.5 cc...	Precipitation	Clear	Precipitation	Clear

A group of experiments was designed to determine whether bile salts interfered with antibody action on pneumococci. It was found that they did not prevent the agglutination or precipitation tests with specific type serums. These results are given in table 4 Controls were run with serums that did not contain bile salts, so that we could be sure that the serums contained specific antibodies. Bile salts did not interfere with these antibody actions. The same results were obtained in a preliminary way in the work represented in table 2. These results are important in consideration of the fact that bile salts are being tried therapeutically. The supernatant fluid obtained by centrifugating the pneumococci out of suspension was used in the precipitation tests. Throughout all these experiments, an 0.85 per cent solution of sodium chloride was used consistently for a solvent in the preparation of suspensions and solutions. In investigating bile salts therapeutically, it would not be expected that they would interfere with natural antibody action. This assumption, of course, arises from the results of the foregoing experiments with agglutinating serum, pneumococci and bile salts.

As the cytolytic effect of bile salts was known, it was desirable to obtain a more definite idea of this effect on normal human blood cells. A dilution series of the bile salts was mixed with equal amounts of washed blood cells (10 per

cent). The cells were washed free from serum by centrifugation and resuspension in salt solution, three times. Table 5 shows the results with the lowest dilutions used. Dilutions from 1 to 5 per cent gave complete lysis within a few minutes. Those from 0.4 to 0.8 per cent gave complete lysis in between thirty minutes and one hour. Complete results with the lesser concentratons are shown in the table. Between readings the tubes were kept in an incubators at 37 C. During these intervals the red cells settled out of suspension to the bottom of the tubes. By the shade of the red in the supernatant fluid and the amount of precipitated cells, one could estimate the amount of lysis that had occurred. The tubes were then shaken and replaced in the incubator.

In comparing these results with those in experiments on pneumococci, represented in table 1, it was observed that bile salts are much more lytic for pneu-

TABLE 5.—*Lysis of Blood Cells in Bile Salts*

	Suspension of Blood Cells Plus Bile Salts			
Bile Salts, %	½ Hour	1 Hour	2 Hours	3 Hours
0.2	Slight lysis	Lysis	Lysis	Lysis
0.1	Slight lysis	Lysis	Lysis	Lysis
0.08	Slight lysis	Moderate lysis	Lysis	Lysis
0.06	Very slight lysis	Slight lysis	Lysis	Lysis
0.04	No lysis	Very slight lysis	Slight lysis	Lysis
0.02	No lysis	No lysis	No lysis	Slight lysis

TABLE 6.—*Effect of Serum on Cytolysis of Blood Cells by Bile Salts*

	Suspension Blood Cells, Cc.	Result	Centrifugation
Plain Nonhemolytic serum, 0.5 cc.	0.5	No hemolysis	Cleared with precipitation
Bile-serum 10 per cent, 0.5 cc.	0.5	Hemolysis	Unchanged

mococci than for red cells. A solution of 0.02 per cent showed only a trace of lysis after three hours in the case of the red cells, whereas a solution of 0.004 per cent (4:100,000) produced some lysis of pneumococci in two hours. Roughly, it can be calculated from this that bile salts are five times more lytic for pneumococci than they are for human blood cells ($0.02 \times 1/.004 = 5$).

Table 6 gives the results in an experiment showing that serum did not prevent cytolysis of blood cells by bile salts.

In order to determine whether serum had some specific protective effect on pneumococci we suspended these organisms in nonagglutinating human serums for fifteen minutes at 37 C. The suspension was then diluted with salt solution. The organisms were thrown down in the centrifuge and the serums poured off. The organisims were then resuspended in salt solution and dilutions of bile salts added. Lysis took place with these serum-exposed organisms just as it did with organisms not so exposed.

Elton[3] has done some work with icterus index determinations in pneumonia. He showed that the icterus index was increased in a series of seventy cases of

3. Elton, N. W.: J. Michigan M. Soc. **28**:451 (June) 1929; New England J. Med. **201**:611 (Sept. 26) 1929.

pneumonia. He also demonstrated that in cases of crisis the highest icterus index occurred either the day before, the day of, or the day after, the crisis. Icterus usually occurred in the latent zone. Fatal cases showed relatively low icterus indexes. If a patient with pneumonia developed a pleural exudate (empyema), the icterus index returned to normal. Influenzal pneumonias did not cause an increased icterus index.

This work led us to assume that icterus in pneumococcus pneumonia was a defensive reaction of the liver on behalf of the body; the liver secreted the bile salts into the blood stream in these cases in an "effort" to damage the pneumococci or to aid in the unknown mechanism by which pneumonia is terminated.

On Jan. 7, 1930, we injected bile salts (sodium taurocholate, Merck) intravenously in a case of lobar pneumonia for the first time, and we have used these treatments in subsequent cases. The drug was dissolved in an 0.85 per cent solution of sodium chloride, filtered and autoclaved before using.

Sodium taurocholate was shown by Emerson [4] to be the less toxic of the two salts. This was to be expected, as the taurocholate molecule contains a sulphate group ($C_{26}H_{45}SO_7N$), whereas the glycocholate molecule ($C_{26}H_{43}O_6N$) does not. Emerson found that the lethal dose of sodium glycocholate was 0.255 Gm. per pound of dog, while that of sodium taurocholate was 0.303 Gm. when given continuously until death.

Our highest therapeutic dose for man was about 0.05 Gm. per pound; and making a direct comparison, the fatal dose would be from five to six times as great as the one we used, or from 0.25 to 0.30 Gm. per pound. Our highest dose was 8 Gm., whereas the calculated fatal dose would be 40 Gm. The greatest total amount given any one patient was 29 Gm. in five days. The doses were 4, 5, 6, 8 and 6 Gm., respectively.

In making our first injections we used concentrated (10 per cent) solutions in a syringe. We found that this produced a chemical phlebitis, with discoloration along the veins and venous obliteration. Subsequent treatments were given with a gravity apparatus in concentrations of from 1 to 2 per cent.

No toxic effects from the drug were noticed. There was no bradycardia and no hemoglobinuria. Blood cell counts showed that some secondary anemia was produced. The respiratory rate seemed to be increased more than one would expect from the disease alone, although we could not be sure of this. We found that the treatments stimulated the flow of bile, causing frequent stools, so that constiuation and typanities did not occur.

Bile has been used from time immemorial as a therapeutic agent, but in recent years has fallen into disuse. The work represented in this paper may stimulate a new interest in bile and bile salts.

Castellanos [5] reported the use of bile salts in treating three children for empyema. He injected the solution directly into the pleural cavity. He also treated a patient with meningitis and one with septicemia

4. Emerson, W. C.: J. Lab. & Clin. Med. **14**:635 (April) 1929.

5. Castellanos y Gonzales, A.: Rev. de med. y cir. de la Habana **34**:133 (Feb.) 1929; Vida nueva **23**:122 (Feb. 15) 1929.

intravenously. He reported good results in this work on the treatment of children for pneumococcus infections.

Having this evidence of the effect of bile salts, we felt justified in using the same treatment in lobar pneumonia in man.

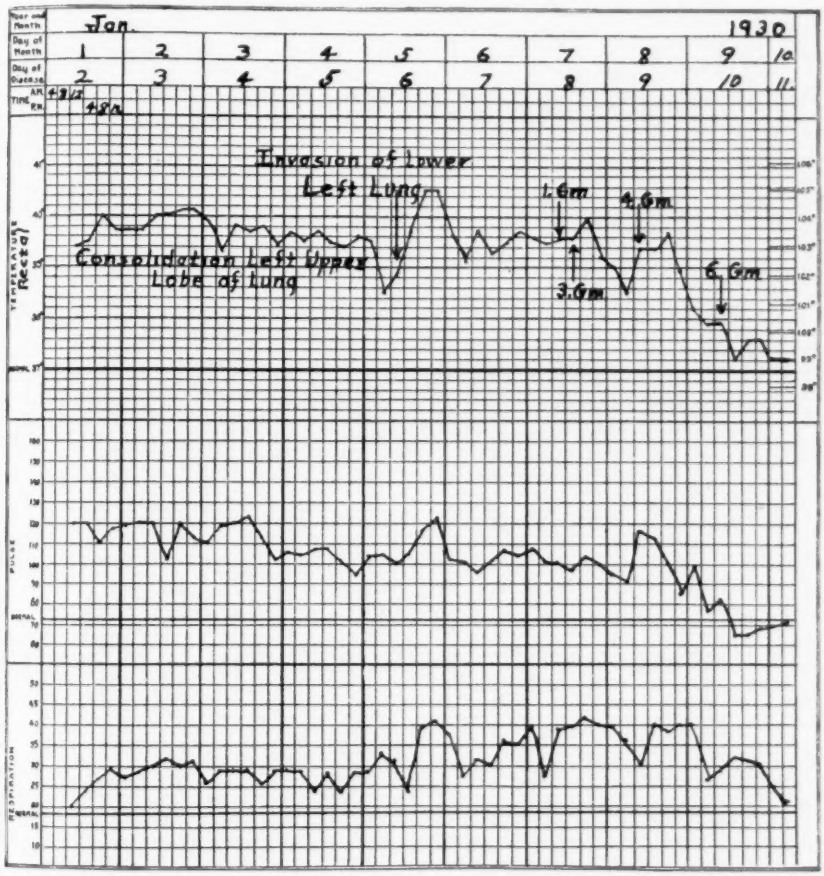

Chart 1.—Clinical data in case 1; dosage of bile salts is given in grams.

REPORT OF CASES

Several case reports follow.

CASE 1.—In the case of E. B., a white man, aged 32, 64 inches (162 cm.) in height and 120 pounds (54.4 Kg.) in weight, the diagnosis was lobar pneumonia and dementia praecox. On Jan. 1, 1930, the patient became ill with chills and fever. There was bronchitis, and the sputum was blood-tinged and contained pus.

The throat was moderately red. The next day there was pain in the left side of the chest; mucous râles were heard over the hili, and there were changed breath sounds over the upper left part of the chest. On January 4, there was definite dulness over the upper left part of the chest and other signs of consolidation. The sputum remained blood-streaked, with much pus present. On January 6, there were signs of extension of the consolidation to the entire left lung. On January 7, the patient's general condition was very unsatisfactory; he was restless and delirious. The entire left lung was consolidated. At 10:45 a. m., we gave the patient 1 Gm. of bile salts in 20 cc. of physiologic solution of sodium chloride. At 4:00 p. m. we gave the patient 3 Gm. of bile salts in 30 cc. of salt solution. On January 8, the patient's condition was somewhat improved, but his left lung remained consolidated. We gave him 4 Gm. of bile salts in 300 cc. of salt solution. On January 9, his condition was greatly improved. Râles of resolution were heard over the entire left side of the chest. At 10:30 a. m. he was given 6 Gm. of bile salts in 300 cc. of salt solution. On January 10, the patient continued to show improvement. On January 11, the clinical chart was normal. He remained well, except for his mental condition which showed little change.

Laboratory examinations by Dr. M. C. Terry showed: on January 2, red cells 4,850,000, hemoglobin 75 per cent, leukocytes 34,600 and polymorphonuclears 90 per cent; pneumococci and staphylococci were present in the sputum; on January 3, leukocytes 27,800 and polymorphonuclears 85 per cent; on January 6, leukocytes 21,800 and polymorphonuclears 82 per cent; on January 7, leukocytes 27,600 and polymorphonuclears 85 per cent; on January 20, red blood cells 2,870,000 and hemoglobin 60 per cent; on January 23, red blood cells 3,250,000 and hemoglobin 65 per cent. Other laboratory reports were negative, including Wassermann and Kahn reactions of the blood and the spinal fluid, urinalysis and examination of the stool.

Case 2.—In the case of M. D., a white man, aged 33, 71 inches (180 cm.) in height and 162 pounds (73.5 Kg.) in weight, the diagnosis was pneumonia, bronchitis, septicemia and manic-depressive psychosis. On Jan. 5, 1930, the patient was received in the infirmary ward. He was quite ill, his face was flushed, his mouth dry, and there was a large amount of thick mucus in his pharynx. The sputum contained blood and pus. There was slight dulness over the upper left part of the chest and a roughening of breath sounds over the hili in the back. On January 6, a positive Kernig sign and a positive Babinski reflex on the left side developed. There was stiffness of the neck. A lumbar puncture was performed showing an initial pressure of 285; the fluid was clear; the Wassermann, Kahn and other tests were negative. Indefinite signs of pneumonia were observed in the chest. The sputum was still blood streaked. The patient's condition was considered grave. The x-ray report stated lobar pneumonia involving the base of the right lung (Dr. J. G. Cullins). On January 7, the patient's neck was stiff, but the positive Kernig sign had disappeared and the reflexes were normal. The sounds in the chest were still indefinite. The patient was brighter mentally. On January 10, the neurologic examination gave negative results. The eyegrounds were normal. The patient was slowly improving. On January 11, he was given 3 Gm. of bile salts intravenously. On January 12, he showed great improvement. He was given 6 Gm. of bile salts intravenously. On January 13, the patient's clinical chart had returned to normal, but he was given 4 Gm. of bile salts intravenously. His clinical chart remained normal. His convalescence was uneventful. The mental condition was unchanged. Laboratory reports furnished by Dr. M. C. Terry showed: On January 5, total leukocytes 17,000, polymorphonuclears 71 per cent, hemoglobin 80 per cent and red blood cells 4,180,000; the urine was normal;

on January 6, leukocytes 23,400, polymorphonuclears 89 per cent; on January 11, pneumococci grown from a blood culture; on January 16, pneumococci from a culture was passed through mice agglutinated by type II serum; on January 20, red blood cells 3,670,000, hemoglobin 70 per cent and leukocytes 7,100; on January 23, red blood cells 4,180,000, hemoglobin 75 per cent and leukocytes 9,200; on March 5, red blood cells 4,200,000, hemoglobin 75 per cent and leukocytes 7,400.

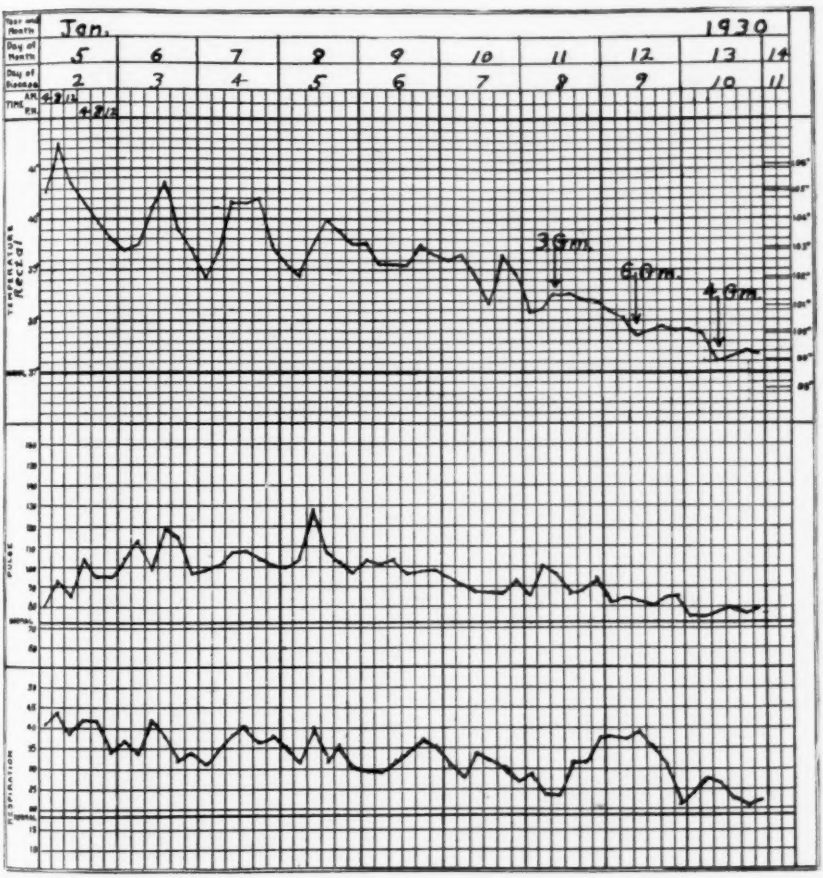

Chart 2.—Clinical data in case 2.

Case 3.—In the case of J. M., a white man, aged 21, 68 inches (172 cm.) in height and 145 pounds (65.7 Kg.) in weight, the diagnosis was lobar pneumonia with pleurisy. The patient was admitted on Jan. 9, 1930, complaining of acute abdominal pain on his left side, which began the previous evening. He had chills and vomited during the preceding night; he presented the picture of an acute abdominal condition. There were, however, beginning signs of consolidation of

the lower left part of the chest. There was tenderness over the upper left part of the abdomen, and pain was produced on palpation of the lower left ribs. On January 10, the patient was given 4 Gm. of bile salts. An x-ray picture of the chest showed increased cloudiness of the base of the left lung (Dr. J. G. Cullins). On January 11, consolidation of the entire left lung was noted. The patient was

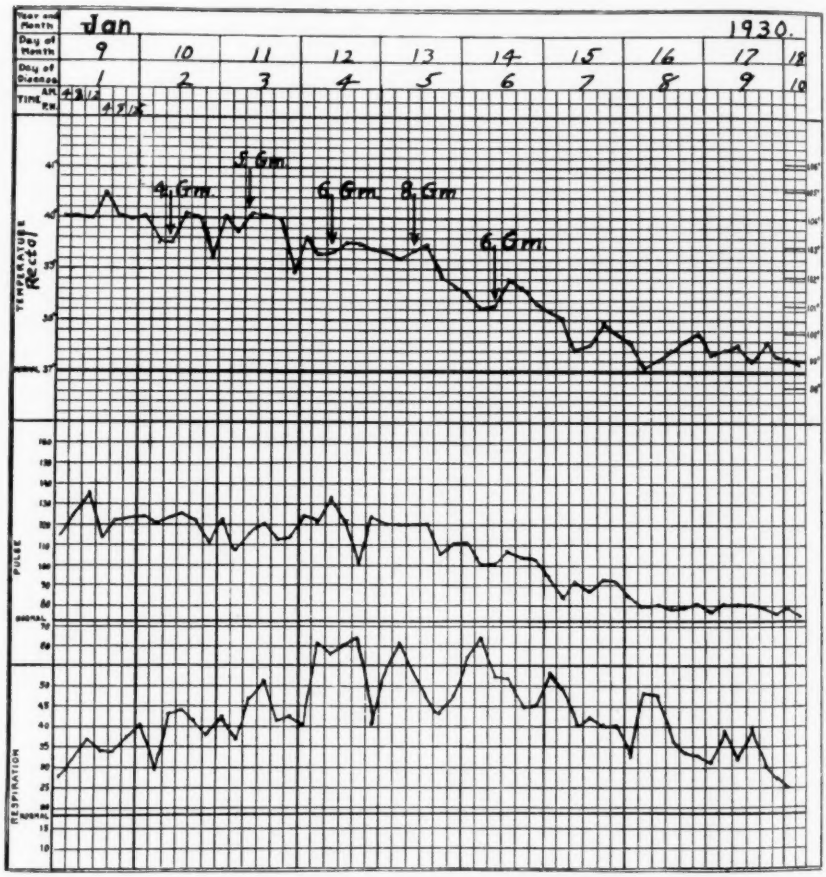

Chart 3.—Clinical data in case 3.

given 5 Gm. of bile salts intravenously. On January 12, he was very ill and semiconscious. There was considerable abdominal rigidity. A pleural rub was heard on the left side as high as the fourth rib. Six grams of bile salts was given intravenously. On January 13, the patient's general condition was much improved. He was brighter mentally. His clinical chart showed improvement. Abdominal rigidity was almost gone, but he still complained of much pain in his left side. He was given 8 Gm. of bile salts intravenously. On January 15 the temperature

became normal for the first time, although it had begun to fall on January 11, which was the third day of the disease (following the second dose of the drug), in spite of the fact that the entire left lung had just become consolidated. Consideration of the temperature curve in relation to the dosage given is significant. A final dose after the temperature became normal was not given in this case to note the effect on the temperature curve. The curve became slightly erratic as before the treatments were given, but remained essentially in the normal range between 99 and 100 F. After January 16, the temperature was consistently normal —not above 99.6 F. The respiration was very rapid, seemingly due to the pleurisy. Sounds of dry pleurisy were the last symptoms to clear up. Convalescence was normal. This patient was a hospital employee.

Laboratory reports by Dr. M. C. Terry showed: on January 9, normal urine; many gram-positive diplococci and possibly pneumococci in the sputum; leukocytes 34,500 and polymorphonuclears 90 per cent; on January 10, normal urine; pneumococci predominating in the sputum; on January 11, leukocytes 13,500 and polymorphonuclears 86 per cent; normal urine with no hemoglobinuria; on January 13, leukocytes 13,800 and polymorphonuclears 85 per cent; on January 14, red blood cells 4,950,000, hemoglobin 75 per cent, leukocytes 18,100 and polymorphonuclears 81 per cent; normal urine, with no hemoglobinuria; on January 16, normal urine, with no hemoglobinuria; organisms from the sputum, passed through mice, were agglutinated by specific serums of type II; on January 23, red blood cells 3,250,000, hemoglobin 65 per cent and leukocytes 8,500; on March 1, red blood cells 4,400,000 and hemoglobin 85 per cent.

It will be noted that in the first case the temperature began to fall following the first dose. This was only two days after an extension of the consolidation from the upper left lobe to the entire left lung. Two more doses were given on successive days and the clinical chart continued to show improvement; the temperature returned to normal and remained there. We did not have serums available to type the organism in this case as we did in subsequent cases, but the organism was identified morphologically and was bile soluble.

The second case began like pneumonia, but consolidation was not detected clinically. This patient had bronchitis. There was a positive blood culture and there were temporary signs of meningitis. An x-ray picture taken with a portable apparatus showed consolidation of the base of the right lung. The sputum contained pus and was streaked with blood. The temperature gradually became lower each day and treatment was instituted very late, but it did produce a change in the form of the temperature curve and brought the disease to an earlier termination.

The third case showed very rapid respirations which remained increased even after the temperature had been normal for some time. This seemed to be due to dry pleurisy which the patient had, and which caused him considerable pain. The rectal temperature returned to 99.6 F. in twenty-four hours following the last treatment. We decided

not to give another treatment in this case, to determine whether the temperature would remain normal. It remained normal with occasional slight elevations of about 1 degree which disappeared after a few days. No doubt, one more injection of bile salts would have been of benefit in this case.

Certain interesting relations were noted between the injections of bile salts and the temperature curve. Following each treatment the temperature would drop, reaching its lowest point from twelve to twenty-four hours after injection of the drug. Temperature readings were made hourly during the daytime following each treatment. This showed that there was a reaction to the drug lasting from one to three hours. The temperature would increase about a degree for this period of time and then would decrease.

The treatments seem to have a tendency to flatten out the temperature curve by removing its erratic fluctuations. The only fluctuations of any extent noted in the curves after treatment, were downward, in contradistinction to upward flucutuations noted in those parts of the curve made when the bile salts were not given.

COMMENT

Further work on this subject is in progress. Lysis of pneumococci by bile salts takes place in serum. The effect of the serum is greatly to retard the speed with which lysis takes place. It is also found that bile salts cause a lysis of blood cells in serum, as well as in salt solution. We have found, as Tatum [6] and others have, that bile salts are cytolytic. They dissolve cells other than pneumococci, namely, blood cells, spirilla, trypanosomes; and probably endothelial and other types of cells.

We have found that bile salts are approximately five times more lytic for pneumococci than they are for blood cells. Considering this fact with the observation that clinical administration produces some anemia, it is reasonable to conclude that bile salts have a lytic action on pneumococci in vivo. That bile salts produce a slight secondary anemia is no contraindication to their use, in consideration of the fact that they aid in the termination of the pneumonic process.

That bile salts are not inert in the human body is shown by the facts that we have observed, namely: They tend to terminate the course of pneumococcus pneumonias; they seem to have a lytic effect in the body on red blood cells, producing a mild anemia; they cause an increased output of bile, and in certain concentrations they damage the veins.

We have shown that bile salts do not prevent antibody action; for when they are added to the specific antiserums, the agglutination and

6. Tatum, A. L.: J. Biol. Chem. **27**:243, 1916.

precipitation phenomena occur just the same. These observations in vitro could almost certainly be applied to conditions in vivo, and especially since clinical results are confirmatory.

From what is known of physiology it would seem that enterotherapy with bile salts would be useless in pneumonia. The salts would be absorbed in the intestine, taken to the liver through the portal system and excreted by the liver into the bile; this is known as the circulation of the bile salts. In view of these facts it would not be expected that the bile salts would enter the general circulation when given by mouth; however, this might be tried.

The damage done to veins by injections of bile salts is considerable. At first it was thought that a 1 per cent solution did not damage the veins; but it was found that even this low concentration eventualiy caused obliteration in the same manner as the new obliterative chemical treatments for varicose veins. No serious interference with circulation resulted. The deep veins and the superficial ones which remained undamaged were sufficient to carry off the venous blood from the arm. However, in one case (no. 3) the left hand became swollen several days following the treatments and then gradually subsided to normal in about a week. The treated veins had become small and sclerotic and had hard nodules, apparently at the valves.

This effect on the veins at the site of, and for some distance above, the injected point seems to be a serious obstacle to the use of the bile salts in pneumococcus pneumonia. In view of the specific effect which the bile salts seem to have on this type of pneumonia, some method of overcoming this defect is being sought. We have not yet determined the p_H of the bile salt solutions, but we know that they are quite alkaline in reaction, and it may be that an adjustment of the p_H of the solutions would help to remove this damaging effect on the veins. Another promising approach to the problem would be the use of other salts or esters of the bile acids instead of the alkaline salts.

It was thought that perhaps dextrose mixed with the bile salt solutions would help to overcome the lytic effect on endothelium.

The lytic effect on blood cells of a series of bile salt solutions, containing dextrose in each per cent from 1 to 20, was determined. The addition of the dextrose to the bile salt solutions made them many times more lytic for washed blood cells than the controls without dextrose. It was also found that the lytic power was increased proportionately to the concentration of the dextrose.

It is known that cholesterol, ordinarily insoluble in water, is soluble in aqueous solutions of bile salts, and also that cholesterol is an "antilytic" agent. Work is to be undertaken with solutions of bile salts and cholesterol.

In consideration of the fact that it is necessary to give the bile salts in dilute solutions to lessen injury to the veins, it would be desirable to use other salts or esters of the bile acids in further experimental work. It may be that other salts or esters of the bile acids could be injected in greater concentrations, with the desired effect of the alkaline salts but without injurious effect on the veins.

SUMMARY

1. Lysis of pneumococci by bile salts (Neufeld's phenomenon) is produced in vitro by extremely weak solutions. In our work, lysis was evident in as dilute a solution as 1:25,000.

2. Neufeld's phenomenon occurs in the presence of serum, but very slowly as compared with its speed in salt solution.

3. Bile salts are approximately five times as lytic for pneumococci as for red blood cells.

4. The exposure of pneumococci to human serum does not interfere with their lysis by bile salts.

5. Bile salts do not interfere in vitro with the antibody (agglutinin) action of specific serums on pneumococci.

6. Intravenous injections of bile salts produce no toxic symptoms. There was no bradycardia and no hemoglobinuria. They have a cholagogue action. They produce a slight degree of anemia.

7. Intravenous injections of bile salts, as used in this work, damage the veins in proportion to their concentration, and tend to obliterate them.

8. Icterus in pneumococcus pneumonia is considered to be indicative of a protective mechanism and not of a toxic phenomenon.

9. Bile salts have been used in the treatment for pneumococcus infections previously, but have been used here for the first time in the treatment for pneumonia.

10. Bile salts seem to have a specific effect in terminating pneumococcus pneumonia.

THE APPEARANCE TIME OF T WAVE CHANGES IN THE ELECTROCARDIOGRAM FOLLOWING ACUTE CORONARY OCCLUSION

REPORTS OF TWO CASES *

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The value of the electrocardiogram has frequently been stressed as an aid in the diagnosis of coronary occlusion. Numerous articles have been written on the similarity of the clinical features of coronary occlusion and acute abdominal conditions requiring surgical measures. Herrick,[1] who was one of the first to call attention to coronary thrombosis as a clinical entity, stated the need of more observations to clear up some of the unsolved problems connected with acute obstruction of the coronary artery. He said: "Clinical and prompt decision as to operation for suspected surgical accidents has to be made at times. Detailed reports of such cases would be helpful."

When the emergency of which he spoke arises, of what value is the electrocardiogram and how soon after the occlusion do characteristic changes take place? A search of the literature has revealed comparatively few cases taken shortly after an attack. Obviously, if the electrocardiogram is to be of value in such cases, the time for it to record the characteristic changes should be within the first twenty-four hours.

Experimentally, Smith [2] found that ligature of the left coronary artery in dogs was followed within from a few minutes to one-half hour by increased amplitude of the T waves. This was later followed by the depression found in human beings following coronary occlusion. Repeated electrocardiograms taken after this showed a gradual return to normal. In human subjects the T wave changes may remain permanent or undergo a return to a more normal state. Parkinson and Bedford [3] expressed the belief that the T wave changes are due to an injury current and explain their transient character in dogs and some human beings as being due to an otherwise healthy heart. Eppinger and

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* From the Medical Department of the Lahey Clinic.

1. Herrick, J. B.: Some Unsolved Problems Connected with Acute Obstruction of the Coronary Arteries, Am. Heart J. **4**:633, 1929.

2. Smith, F. M.: The Ligation of the Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

3. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram on Coronary Thrombosis, Am. Heart J. **4**:195, 1928.

Rothberger,[4] in 1909, injected silver nitrate into the basal ventricular muscle and within five minutes found an increased height of the T wave and within fifteen minutes high take-off or R-T fusion. They did not follow their experiments through as did Smith, but the results are essentially the same. Application of cold by means of ethyl chloride to the same region produced immediate inversion of the T wave. The increased amplitude of the T wave is thus explained by an injury current set up at the time of the infarction augmenting the normal electrical currents, whereas depression of the normal electrical currents, such as follows infarction at a later period or by the immediate application of cold, produces inversion of the T waves.

In table 1 are grouped the cases reported in the literature and my own cases in which electrocardiograms were recorded during the attack or within eight hours afterward. Definite time relationships are often not given; a knowledge of them would be of value in the study of this problem. In only one case besides mine was an electrocardiogram taken before an attack at an interval of less than three weeks (case 6, Willius and Barnes).

During the attack, the records in their case showed more pronounced changes; i. e., a lower T wave in lead I and fusion of the R-T waves in leads II and III. The electrocardiogram in case 7 (Willius and Barnes) taken during the attack showed an inversion of the T waves in leads II and III. This patient, however, had had a previous coronary attack, so that it is impossible to say without subsequent observation whether or not the T wave changes in this record were produced by the attack at that time or by the one a few months before; twenty-four hours later, however, there was inversion of the T waves in all leads. In case 9 (Willius and Barnes) an electrocardiogram taken fifteen minutes after the onset showed no changes, but here again, twenty-four hours later, the T waves were inverted with right bundle branch block.

In case 19 of Parkinson and Bedford an electrocardiogram taken at onset showed upright T waves in all leads. Twenty-four hours later, the T waves in leads II and III were inverted. No record was taken before the attack. In Smith's [2] case a record taken six hours after onset showed an inverted T wave in lead I, which again is open to the foregoing criticism, as no electrocardiogram was recorded beforehand. Furthermore, there was no appreciable change twenty-four hours after the attack. Nathanson's case was somewhat similar. In Pardee's [5] case a record taken four hours after the onset of the attack showed character-

4. Eppinger and Rothberger: Zur Analyse des Electrokardiogramms, Wien. klin. Wchnschr. **22**:109, 1909.

5. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**:244 (Aug.) 1920.

TABLE 1.—*Cases in Which Electrocardiograms Were Taken During the Attack or Within Eight Hours Afterward*

Author	Author's Case No.	Previous Attack or Symptoms	Electrocardiogram Before Attack	Time After Onset Electrocardiogram Was Taken	Changes in T Wave
Parkinson and Bedford: Am. Heart J. **4**: 195, 1928	19	Angina pectoris	0	At onset.....	Upright T1, T2, T3
				2 weeks after...	Inverted T2, T3
Willius and Barnes: J. Lab. & Clin. Med. **10**: 427, 1924	4	Previous attack	0	At onset.....	Low, but upright T2, T3
	6	Angina pectoris	2 days before	.....	Inverted T2, T3
				During attack.	Inverted T2, T3, lower T1; fusion of R-T in leads 2 and 3
				Day after.....	Inverted T1 (plus previous changes)
	9	0	0	15 min. after attack	Upright T1, T2, T3
				24 hours after attack	Inverted T1, T2, T3; right bundle branch block
	7	Previous attack	0	During attack,	Inverted T2, T3
				Next day.....	Inverted T1, T2, T3
Smith: Arch Int. Med. **32**: 497 (Oct.) 1923	3	Not stated	0	6 hours after onset	Inverted T1
				24 hours later	Inverted T1
Nathanson; quoted by Willius and Barnes	..	Not stated	0	4 hours after onset	Inverted T1, T2
Pardee: Arch. Int. Med. **26**: 244 (Aug.) 1920	..	Probable angina pectoris	0	4 hours after onset	Inverted T1; fusion of R-T in leads 2 and 3
Levine: Personal communication	61	Angina	0	*Same day.....	Low, but upright T1
				24 hours later..	Low T1, fusion of R-T2 and inverted T3
	56	0	0	Same day.....	High take-off of T waves
	133	0	0	? 5 hours after attack	Upright T1, T2, T3
				? Next day.....	Beginning depression of T waves
Rothschild, Mann and Oppenheimer: Proc. Soc. Exper. Med. & Biol. **23**: 253, 1926	1	Not stated	..	6½ hours.....	High origin, lead II (only one shown)
				6 days.....	Lower origin
				14 days.....	Inversion of T
Hurxthal	1	Nocturnal dyspnea	6 days before	.....	Inverted T1
				1 hour.....	Upright T1, T2, T3; low takeoff T1
Hurxthal	2	0	9 days before	.....	Upright T1-T2, inverted T3
				1 hour, ... 15 min.	Higher T1, lower T2, deeper T3
				4 hours, ... 5 min.	Higher T1, deeper T3
				14 hours	Same as previous tracing
				38 hours.....	Inverted T2
				16 days	Inverted T2
				27 days.....	Less marked inversion of T2

* It is assumed that records taken the same day were probably taken within eight hours.

istic changes. From the history of this case it is probable that the patient had had previous trouble, so that one cannot be absolutely sure of the significance of this record as regards the attack in question. Levine's[6] case 133 showed upright T waves in all leads five hours after the attack, but twenty-four hours later showed beginning changes.

The other two cases reported by Levine, in which records were taken on the same day of the attack, both showed upright T waves; one exhibited a low T in lead I, later followed by fusion of the R-T in lead II and inversion in T3, and the other immediately showed fusion of R-T waves in all leads. In the case reported by Rothchild, Mann and Oppenheimer, a record taken six and one-half hours after the onset showed fusion of the R-T wave in lead II, which was followed in fourteen days by inversion of the T wave in lead II.

In the cases herein reported an attack developed while the patients were under observation in the hospital. Case 1 is of particular interest in view of the practically normal electrocardiogram taken one hour after onset in spite of an abnormal tracing taken in the hospital six days before. It might be considered analogous to the experimental work of Smith, Eppinger and Rothberger. The one complicating feature, however, was the administration of digitalis in the interim. Had this been a case in which an acute surgical condition in the abdomen had been suspected and had no tracing been taken beforehand, the electrocardiogram would have been decidedly misleading (figs. 1 and 2).

The electrocardiogram in case 2, taken one hour and fifteen minutes after the attack, showed a slight change in the electrical axis, a slight dip in the T wave of lead II and a marked inversion of T3. These can probably be considered significant in the light of subsequent events, although definite inversion of the T wave in lead II was not noted until fifty-six hours after onset. The increased amplitude of the T wave in lead I might have been due to the same mechanism as in case 1, but the release of thyroid secretion following operation might also have caused it.

In summarizing the cases in table 1 taken within six or seven hours of the attack, it is to be noted that eight showed upright T waves in all leads and that six of these were known later to have been followed by inversion of the T wave. Only two of these showed R-T fusion alone as the first sign. There was a history of previous angina pectoris or coronary occlusion in three of these eight cases, but none in four; in one case the history was not known. Five of these cases showed inversion of the T wave in records taken within seven hours. Three of these patients probably had a history of previous pain in the heart, whereas in two the past history was not mentioned.

6. Levine, S. A.: Personal communication to the author.

Thus, of fourteen patients, six can be considered to have had electrocardiograms that were not diagnostic, two had only high take-offs of T waves ("R-T fusion" "Cove plane T") and six had definitely inverted T waves. In view of the fact that three of the latter patients had an antecedent history of cardiac pain, it is obvious that these records cannot be considered diagnostic of the attack following which they were taken. The Cove plane T is considered by various authors as the first change following coronary occlusion; its value as an early sign is limited in view of the fact that it occurred only four times in these thirteen cases.

It cannot be denied that if T wave changes are found within six or seven hours after the onset of an attack, they are highly suggestive, but

TABLE 2.—*Cases in Which Electrocardiograms Were Made About Twenty-Four Hours After the Onset of the Attack*

Author	Author's Case No.	Previous Attack or Symptoms	Electrocardiogram Before Attack	Time After Onset Electrocardiogram Was Taken	Changes in T Wave
Parkinson and Bedford	9	.....	0	Next day after attack	Low T
Smith: Arch. Int. Med. 32: 497, 1923	2	Not stated	0	24 hours after	Inverted T1
Wearn: Am. J. M. Sc. 165: 250, 1923	..	.....	0	Day after.....	Diaphasic T3
Levine: Medicine 8: 246, 1929	15	0	0	Next day.....	Inverted T waves
	11, 20, 33, 140	Angina pectoris	0	Next day.....	Inverted T waves
	10	Angina pectoris	2 years before	.....	Not remarkable
				Day after attack	High origin; low T; inverted T3
Hurxthal	9229	Angina pectoris	0	15 hours.....	Inverted T1; slurring QRS (died)
	368	Indefinite	1 year	18 hours.....	Upright T2 and T3; inverted T1; flat T2

on the other hand they may be entirely absent, may appear to be normal (as in case 1) or may have existed beforehand. Progressive changes will be found in most cases by the end of twenty-four hours, or possibly sooner, or comparisons may be made with records taken beforehand.

In table 2 I have listed my own cases and those reported by others in which records were taken about twenty-four hours after the onset of the attack. Undoubtedly some may have been taken before that time, but, as a rule, the time stated was the next day. It is to be noted that all the cases in the latter group (table 2) showed definite T wave changes. Wearns' case showed only a diaphasic T wave in lead III. Parkinson and Bedford commented on T wave changes in lead III and stated that they believed a marked inversion of T3 highly suggestive of coronary disease. One of their cases showing only this feature was followed up, and subsequent records showed progressive changes. This

was true of case 2 reported here; thus the interpretation of marked inversion of the T waves in lead III probably can be of definite significance only if successive records are made.

So far as can be determined, case 1 herein reported is the first one to be described which closely parallels the experimental work of Smith, Eppinger and Rothberger. It is likely that if more records had been obtained before the attacks in those cases that showed upright T waves, a distinct change in the amplitude of these waves might have been noted. It is hoped that more frequent observations will be made and reported during the first twenty-four hours, especially in those cases in which previous records have been obtained.

One must therefore rely chiefly on clinical observation in doubtful cases to make the diagnosis of acute coronary occlusion if a prompt decision must be made. Serial electrocardiographic observations at hourly intervals, however, may prove helpful.

REPORT OF CASES

CASE 1.—Mrs. F., a housewife, aged 53, had been in good health up to the onset of the present illness, which began gradually with symptoms of weakness, loss of energy and exhaustion. She had been under an emotional strain from the death of her husband, and under a physical strain from lack of sufficient rest during attacks of pneumonia and subsequent influenza during the previous winter. In January her exhaustion required rest in bed. She grew weaker slowly throughout the spring, and in April had an attack of pain in both arms and later in the legs, which her physician thought to be multiple neuritis. This pain disappeared after about a month, and she had not been bothered with it recently. One month before admission she noticed edema of the ankles and the feet, which persisted. A week or so before admission she noticed nocturnal dyspnea for the first time, and this persisted up to the time of admission. Orthopnea had been present during the same period. She had no cough or precordial pain. Within the previous month a few purpuric lesions appeared without known trauma. Her greatest distress was at night when she had trouble in breathing. She was admitted to the hospital on June 14, 1929.

On physical examination the patient appeared to be well developed but rather pale. The examination of the left eyeground showed marked vascular changes with numerous new hemorrhages and evidence of old ones. The right fundus was not clearly distinguished. Numerous teeth were missing. The thyroid gland was not enlarged. The lungs were clear. The heart was markedly enlarged; the rate was rapid but regular, and there was a systolic murmur at the apex. The abdomen was normal. There was slight pitting edema of the ankles. The blood pressure was 220 systolic and 110 diastolic. A teleoroentgenogram of the heart showed the apex to be opposite the sixth rib anteriorly, 10.6 cm. to the left of the median line. The right border of the heart was 4.2 cm. to the right of the median line. The long diameter of the heart was 15.6 cm.; the diameter of the base was 9.4 cm. The diameter of the great vessels was 6.2 cm. The total width of the chest on the level with the apex of the heart was 23.5 cm. Slight scoliosis of the dorsal spine with the convexity to the right was evident. Examination of the urine revealed a trace of albumin and a specific gravity of 1.010;

microscopic examination revealed one or two fine granular casts and an occasional red cell and white cell to each high power field. The two hour renal test showed a fixation of specific gravity between 1.010 and 1.016. The output of urine during the night was 230 cc.; this showed a specific gravity of 1.016. The two hour renal function phthalein test showed 35 per cent; the nonprotein nitrogen measured 39 mg. per hundred cubic centimeters of blood; the red blood cells numbered 5,010,000, and the white blood cells 13,000; the hemoglobin content was 75 per cent.

On the day of admission an electrocardiogram was taken (fig. 1). The following two days the patient received 24 grains (1.5 Gm.) of digitalis (powdered leaves). After a few days, the edema of the ankles cleared up and the patient thought she slept better at night, with less difficulty in breathing. On the morning of June 20 (six days after admission), the patient was seen as usual; the blood

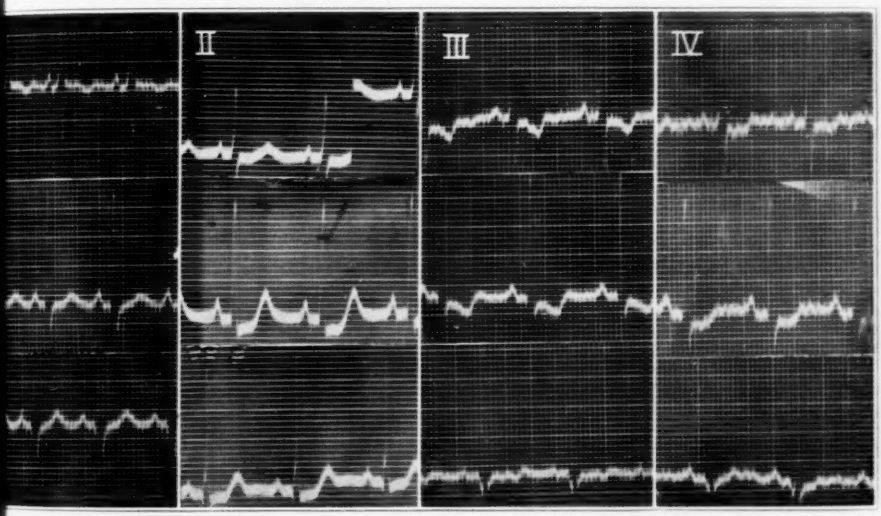

Fig. 1.—Tracings in case 1: I, June 14, 1929 (six days before attack); II, June 20 (one hour after onset); III, June 22, and IV, June 24.

pressure was 210 systolic and 105 diastolic. Shortly afterward, the patient was given a bedpan. While on this she suddenly collapsed and became very weak and short of breath. She complained of no particular pain. Her pulse was very weak, she showed marked pallor, her skin was cold and clammy, and she perspired profusely. Her blood pressure taken immediately after this was 88 systolic and 52 diastolic. A fourth of a grain (0.016 Gm.) of morphine was given hypodermically. Just before the injection the patient was conscious of a little pain over the region of the heart.

After the hypodermic injection an electrocardiogram was made, which is shown in figure 1 (II). The patient's condition gradually improved, but during the next two days she had an almost complete suppression of urine, with the recurrence of edema, slight tenderness of the liver and pitting edema of the sacrum. Subsequently the condition improved, and the blood pressure gradually rose to its

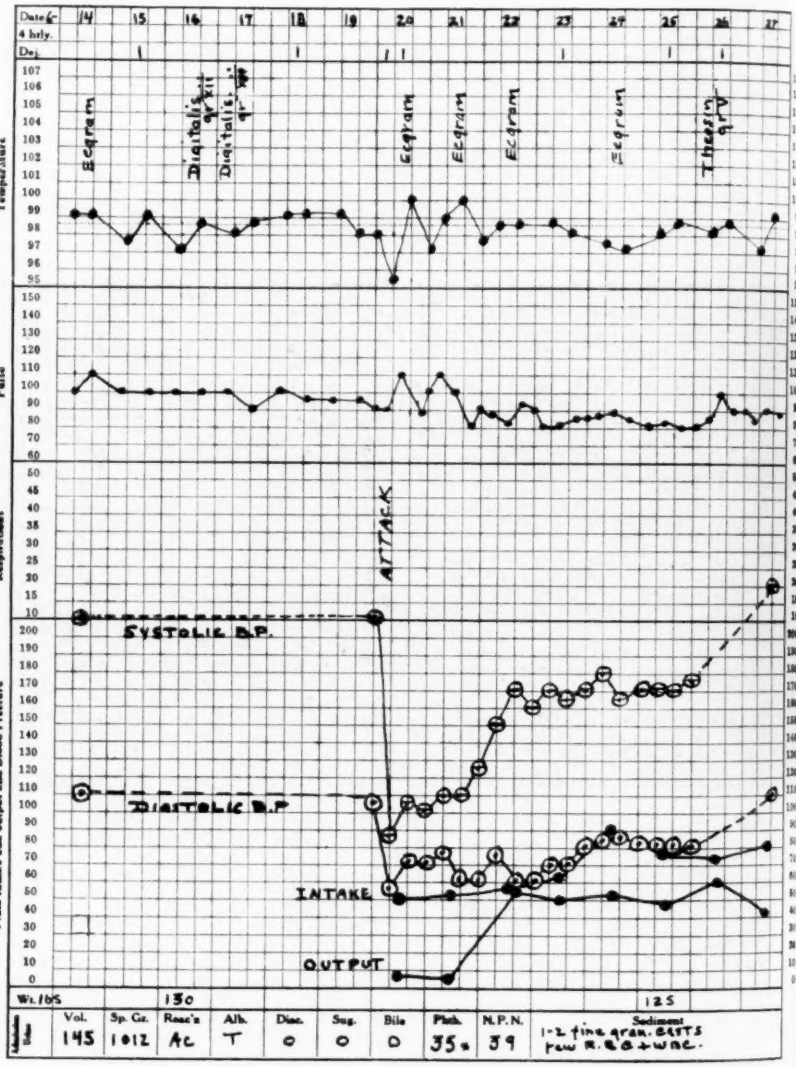

Fig. 2.—Clinical chart in case 1.

previous level; when she was discharged from the hospital, approximately one month later, her blood pressure was 220 systolic and 105 diastolic (fig. 2).

She progressed fairly well at home until about three months later, when she experienced another similar attack from which she recovered. When last seen, she was up and about, but was almost completely blind.

CASE 2.—A single woman, aged 59, came to the clinic on Nov. 22, 1929. Her past history was essentially unimportant except for scarlet fever in childhood. She complained chiefly of shortness of breath and nervousness for the past year. For the last few months she had been taking medicine for high blood pressure.

Examination showed a well developed woman with good color. Physical examination revealed the absence of teeth. The eyegrounds showed slight compression of the veins and marked tortuosity of the vessels. The blood pressure

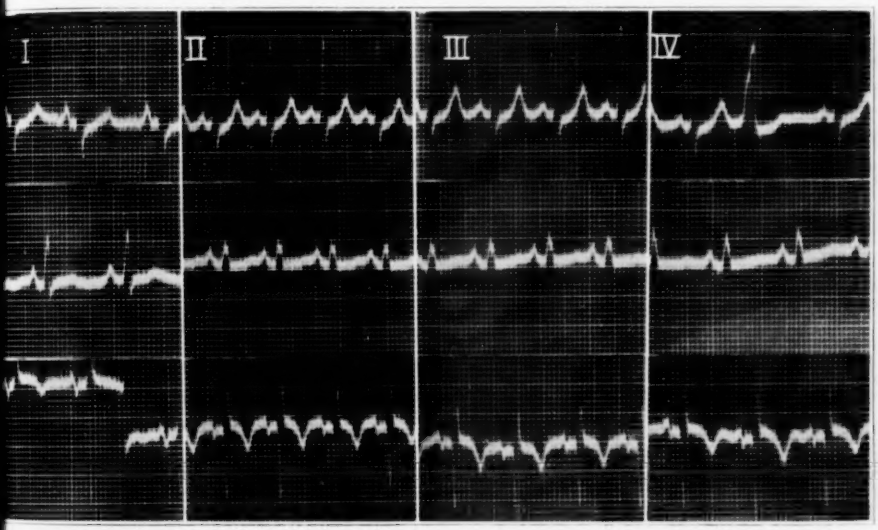

Fig. 3.—Tracings in case 2: I, Nov. 25, 1929 (before onset); II, December 4 (one hour and fifteen minutes after onset); III, four hours and five minutes after onset, and IV, December 5 (fourteen hours after onset).

was 155 systolic and 100 diastolic. The skin was warm, and there was a slight tremor. The heart was moderately enlarged, showing numerous extrasystoles. The lungs were clear; the abdomen showed nothing abnormal; the legs revealed moderate-sized varicose veins. The patient was slightly deaf in both ears. The thyroid showed a nodular enlargement on the left side, extending below the clavicle. Roentgen examination of the trachea showed it to be markedly deviated to the right.

The patient was sent to the hospital for observation and decision as to operation. The electrocardiogram taken at that time is shown in figure 3. The basal metabolic rate was +21 per cent; the pulse rate, 70; the weight, 154 pounds (69.8 Kg.), and the blood pressure, 170 systolic and 90 diastolic. A teleoroent-

genogram of the heart gave the following measurements: The apex was opposite the seventh rib anteriorly, 12.5 cm. to the left of the median line. The right border was 5 cm. to the right of the median line. The diameter of the lung was 17.8 cm., and the diameter of the base, 9.2 cm. The diameter of the great vessels was 7.9 cm. The width of the chest at the level of the apex was 26.8 cm.

Examination of the urine showed a specific gravity which ranged from 1.020 to 1.030. There was a light precipitate of albumin at all examinations. The sediment was negative. The phthalein excretion was 40 per cent in two hours and ten minutes. On several occasions there was from 0.1 to 0.3 per cent sugar in the urine. The fasting blood sugar was 0.1 per cent. The nonprotein nitrogen was 32 mg. per hundred cubic centimeters of blood. The Wassermann reaction was negative.

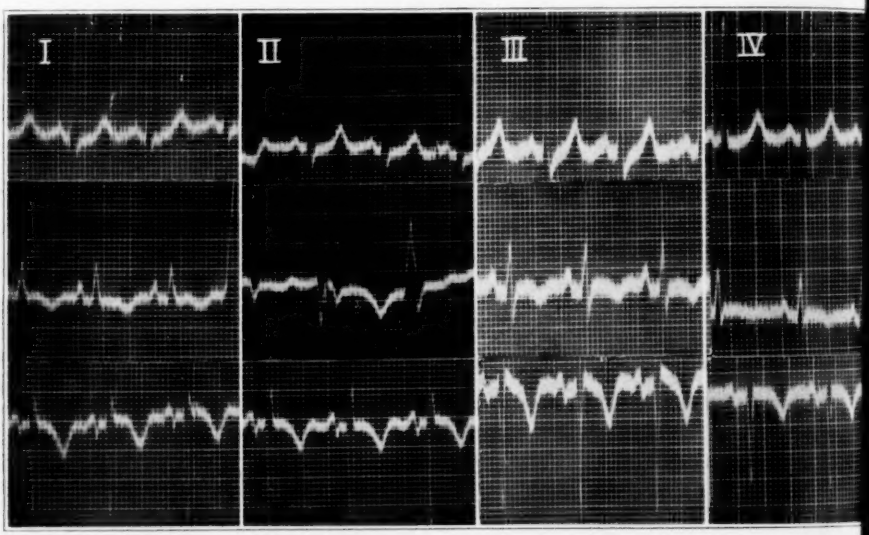

Fig. 4.—Further tracings in case 2: I, Dec. 6, 1929; II, December 7; III, December 20, and IV, December 31.

The patient was operated on, Nov. 29, 1929. The left lobe of the thyroid was found to be about eight times the normal size, with a much enlarged isthmus. The trachea was deviated markedly to the right. A left subtotal thyroidectomy was performed. The patient went through the operation without incident, and did well until December 5. Following an enema and the use of the bedpan, the patient was seized with marked dyspnea and orthopnea, and profuse sweating. No pain was experienced. The blood pressure was 120 systolic and 95 diastolic and the heart rate was rapid with a gallop rhythm and occasional extrasystoles. An electrocardiogram was taken an hour and fifteen minutes later (figure 3 [II]). The patient was given morphine, and electrocardiograms were taken on subsequent dates (figs. 3 and 4). The patient recovered satisfactorily and was transferred to her home three weeks after the date of the attack (fig. 5).

Fig. 5.—Clinical chart in case 2.

She was seen again four weeks after the attack, at which time her blood pressure was 170 systolic and 110 diastolic. Extrasystoles were present. The patient was having no trouble, although her activity had been markedly restricted. The electrocardiogram taken at this time is shown in figure 4.

SUMMARY AND CONCLUSIONS

1. The value of the electrocardiogram in the diagnosis of coronary occusion has been repeatedly emphasized.

2. Experimental work cited shows that increased amplitude of the T wave follows ligation or injury to the muscles supplied by a coronary artery; cooling causes depression of the T wave.

3. Case reports from the literature have been reviewed; twelve cases were found in which records were taken within eight hours after an attack of coronary thrombosis. Only one patient had a record taken within three weeks before an attack.

4. Two cases are reported in which records were obtained before and after attacks. Case 1 showed upright T waves in all leads one hour after the onset of the attack, later followed by depression, whereas the record six days before the attack showed an inverted T wave in lead I. Case 2 showed a distinct but not diagnostic change one hour and fifteen minutes after onset.

5. Eight cases in the literature showed upright T waves within eight hours after onset. Only four showed R-T fusion, and six showed inverted T waves.

6. Seventeen cases showed definite T wave changes taken the day after the attack.

7. Single tracings immediately following acute coronary occlusion may appear normal, or if abnormal are of little value unless previous records have been taken or later records are obtained.

8. At present, one must rely on clinical diagnosis rather than on the electrocardiogram in an emergency in which surgical measures are considered.

9. It is suggested that electrocardiographic observations be made at more frequent intervals following acute coronary occlusion. Such observations may prove of distinct value in diagnosis.

EVALUATION OF THE EXPULSION OF ENEMAS AS A CRITERION OF INTESTINAL OBSTRUCTION*

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The persistently poor results obtained by surgeons in acute intestinal obstruction are in a large measure due to delay in diagnosis. Clinicians have been disposed to place a good deal of reliance on the expulsion of an enema as evidence militating against the presence of mechanical obstruction in the bowel, and there exists a general unwillingness to accept the diagnosis of acute obstruction of the intestine as long as enemas continue to be returned with the expulsion of gas and feces.

In this study an attempt has been made to evaluate the significance of the expulsion of enemas as a criterion of intestinal obstruction.

In a series of nine dogs, obstructions of varying types were established, and Noble's enemas were subsequently administered. In four animals a high jejunal complete obstruction was established by severing the bowel and inverting the proximal end; the distal end was brought up and anchored to the skin. In another dog a low complete ileal obstruction was established, and in two others partial obstructions were made by ligating the bowel with gauze. In two other animals a strangulation obstruction was made by tying off with gauze about 3 feet (0.9 meter) of the intestine together with its mesentery.

In the partial and strangulation types of obstruction a urethral catheter was placed into the distal bowel by the Witzel enterostomy technic. As the accompanying table indicates, dogs in which complete obstructions have been established, as well as animals having partial obstructions or strangulation obstructions, regularly expel enemas on their administration.

Barium sulphate was injected through the catheter into the distal loop of a number of animals, and the transit of barium through the bowel was followed by roentgenograms. The rate of transit of barium through the distal bowel is apparent from the table. In most cases the time of transit was normal; in a few cases it was delayed. In a few of the x-ray films a spastic contraction of portions of the distal loop was noted.

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* From the Department of Surgery, University of Minnesota.

Since these observations were made, Carlson and one of us (O. H. W.) [1] have tried to establish a comparison of the peristaltic activity of the various segments of the bowel in intestinal obstruction. By passing a small inflated balloon into the intestine distal to the obstruction a better quantitative estimate may be obtained of the ability of this segment to contract in dogs with intestinal obstruction. In the dogs in which the peristaltic activity was measured in this manner, it was soon apparent that definite peristaltic contractions could be elicited. Comparison with the peristaltic activity of the normal dog's intestine demonstrated a quantitative reaction of approximately the same charac-

Expulsion of Enemas in Intestinal Obstruction

Dog	Type of Obstruction	Length of Survival, Days	Number of Enemas	Number of Evacuations Containing Gas and Feces	Barium Sulphate Injected	Condition of Distal Bowel Post Mortem	Approximate Number of Hours Before Barium Sulphate Appeared in Stool
1	High complete obstruction; inversion method with enterostomy	4	1	1	+	Normal	6
2	High complete obstruction; inversion method with enterostomy	7	4	3	+	Spastic	6
3	High complete obstruction; inversion method with enterostomy	6	4	3	+	Spastic	24
4	High complete obstruction; inversion method with enterostomy	5	3	3	+	Semispastic	5
5	Complete low obstruction; no enterostomy	5	4	4	0	Flaccid	..
6	Low strangulation obstruction with Witzel enterostomy	1	2	2	+	Semispastic	..
7	High strangulation obstruction with Witzel enterostomy	1	2	2	+	.....	..
8	Low partial obstruction with Witzel enterostomy	..	3	3	+	.....	..
9	Low partial obstruction with Witzel enterostomy	2	2	2	+	Normal	6

ter. The obstructed loop, however, exhibits greater contractile power than either the normal intestine or the segment distal to the point of obstruction. The latter segment reacts to subcutaneous injections of pilocarpine hydrochloride or solution of pituitary much as does the normal segment; the reaction of the obstructed segment to similar drugs is much more intense, however.

During the time that these experimental observations have been carried on, we have had adequate opportunity to observe similar behavior in the segment of bowel beyond the obstruction in the human being.

1. Carlson, H. A., and Wangensteen, O. H.: Motor Activity of the Distal Bowel in Intestinal Obstruction: Comparison with the Obstructed and Normal, Proc. Soc. Exper. Med. & Biol. **27**:676-681, 1930.

Unless the patients have had several rectal irrigations before coming to the hospital, the administration of an enema will be regularly returned with flatus and feces unless the obstruction is complete and low in the colon. Following repeated enemas, no return of gas or fecal matter will occur when the obstruction is complete and the lower bowel has become completely evacuated. In incomplete obstructions of the bowel gas will continue to be obtained, though often in small amounts. During the time that preparation is being made for operation, we have, on a

Fig. 1.—Roentgenogram of the abdomen of a dog with severed intestinal obstruction after injection of barium sulphate into the distal loop. A portion of the bowel appears to be contracted in spasm.

number of occasions, had flat x-ray films made of the abdomen before and after the administration of enemas to serve as a visual record of what the attendant observes at the patient's bedside. In incomplete obstructions of the small bowel, a diminution of the gaseous collections in the small intestine may be noted with progression into the colon.

It is easily apparent, therefore, that the expulsion of enemas cannot be a safe guide to the presence or absence of interference with the con-

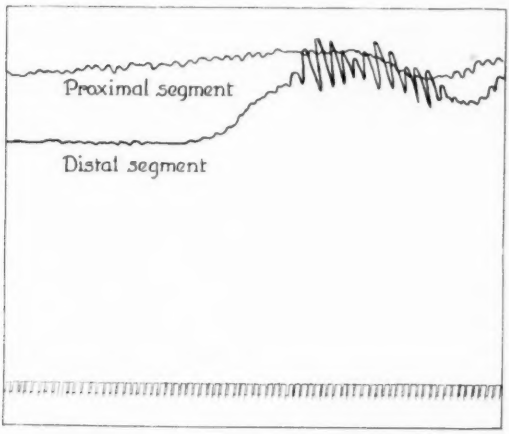

Fig. 2.—Drawing from a tracing obtained by placing rubber balloons into the intestine. Five hours previously a severed intestinal obstruction had been established. The distal segment appears even more active than the proximal.

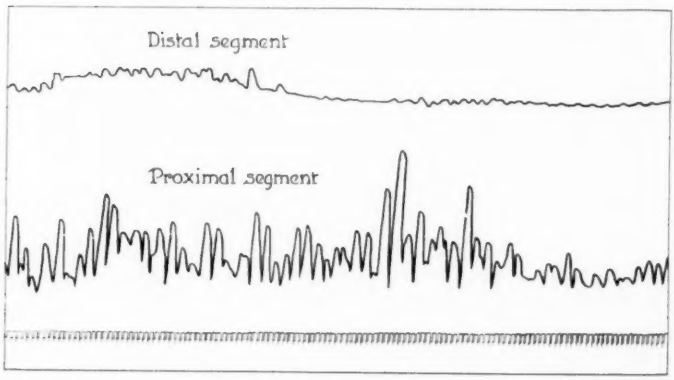

Fig. 3.—Similar tracing made from a dog with severed intestinal obstruction of seven days. The peristaltic activity of the obstructed bowel is unusually great for an obstruction of that duration.

tinuity of the bowel. Failure to obtain a return of gas with a second enema usually indicates that the obstruction is complete; return of flatus, however, does not militate against the presence of obstruction. The distal bowel in intestinal obstruction is anatomically and physiologically normal. Why should it not expel gas? Failure to recognize obstruction of the bowel because the occlusion is incomplete is not an infrequent occurrence, but to defer operation deliberately in acute intestinal obstruction because the block is incomplete is a dangerous responsibility.

When this concept of the "blocked bowel" as a criterion of intestinal obstruction is generally appreciated, patients will come to operation considerably earlier. Procrastination until the block in the bowel is

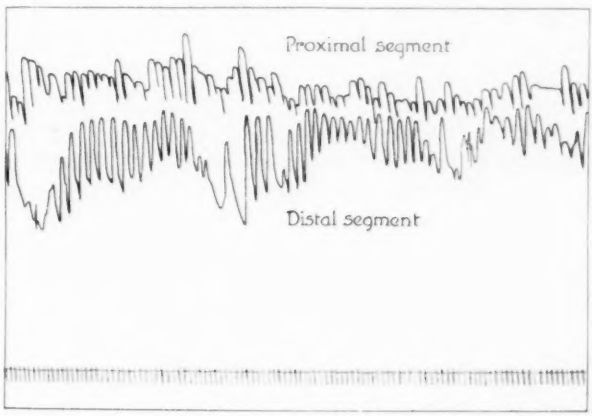

Fig. 4.—Tracing made from a dog with a severed intestinal obstruction of six days' duration. The tracing was obtained under spinal anesthesia. The activity of both the obstructed and unobstructed intestine is great.

absolute is to await confirmation of these signs of obstruction that indicate that precious time and irretrievable opportunity have been lost.

In this communication relative to the employment of enemas as a criterion on which judgment is passed as to the existence of intestinal obstruction, no attempt will be made to elaborate the method of making an early diagnosis. We should like to refer briefly, however, to the criteria on which we believe such an opinion may be arrived at early.

When a mechanical block [2] exists in the bowel, there are no local physical observations that help to corroborate the suspicion that the

2. Strangulation obstructions in which the blood supply to a portion of the intestine is compromised, however, produce local physical observations.

patient has acute intestinal obstruction. In all the disasters or catastrophies of an acute nature to which the abdomen is heir, with the single exception of intestinal obstruction, definite local observations that at least suggest the necessity for surgical intervention are present. Local tenderness, rigidity or muscle spasm is absent. These facts may be presented in extenuation of the late recognition of most instances of acute obstruction of the bowel. At the same time the occurrence of intermittent, crampy, colicky, abdominal pain followed by nausea and reflex vomiting without local physical observations should immediately suggest the possibility of intestinal obstruction.

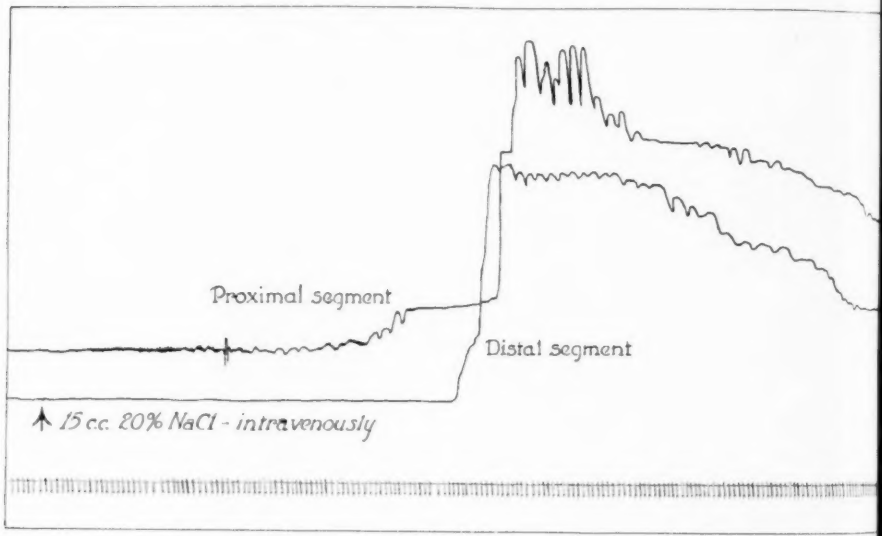

Fig. 5.—The effect of the intravenous injection of hypertonic solution of sodium chloride. A similar response is obtained from the bowel distal to the obstruction as is observed in the obstructed intestine.

Visible peristalsis, though observed in almost every instance of subacute or chronic intestinal obstruction, is rarely seen in acute obstruction. The auscultation of the abdomen, however, gives evidence of real value. In the absence of visible peristalsis, loud peristaltic rushes like the bubbling sound produced by pouring water out of a bottle may be heard with the stethoscope when a mechanical obstruction exists. A dilated intestine in which considerable fluid and air are present is necessary to elicit these bubbling sounds. Near the point of intestinal occlusion these intestinal noises may attain explosive force. Frequently a metallic tinkle may be heard, a sign of conclusive significance for the

existence of mechanical obstruction. As the fluid and air are carried down toward the point of obstruction by peristaltic rushes, their progress is suddenly arrested, and fluid and air which were intimately mixed in their advance tend to separate as the onward movement is halted. As the air rises to the surface, a sound like drops of water falling in a rain barrel may be heard. The metallic character of the sound has a high pitch imparted by the tension of the dilated intestine. In mechan-

Fig. 6.—Roentgenogram of the abdomen of a dog four and one-half hours after a simple severed intestinal obstruction had been established in the ileum. The gaseous distention of the intestine proximal to the obstruction is apparent.

ical obstruction of the intestine, this metallic tinkle can be detected before the bubble noises referred to are audible. Such sounds may also frequently be heard over the abdomen after an abdominal operation when recovery from the paresis of the intestine incident to the operation begins.

Pain, vomiting, collapse, constipation and meteorism have been the usual standards on which judgment has been based as to whether or not

obstruction of the bowel exists. All of these phenomena may be observed at some time during the course of intestinal obstruction, but their importance as measures of diagnostic value must be properly appraised. In his nonpareil text on the principles and practice of medicine, the late Sir William Osler [3] says, "The sequence of gastric, bilious, and finally stercoraceous vomiting is perhaps the most important diagnostic feature of acute obstruction." That this in part is true must be freely conceded, but it is decidedly unsafe to await confirmation

Fig. 7.—The same dog after ten hours.

of this succession of events. Similarly, absolute constipation, meteorism and collapse may establish the diagnosis, but at a time when the patient is beyond hope and remedy. Regurgitant vomiting and abdominal distention are rather to be considered as heralds of death than as symptoms of acute intestinal obstruction.

3. Osler, William: Principles and Practice of Medicine, ed. 8, New York, D. Appleton & Company, 1918, p. 542.

Long before clinical distention is apparent, an x-ray film of the abdomen will reveal intestinal dilatation. Satisfactory roentgen demonstration of gaseous shadows in the small intestine in a patient who has intermittent crampy pain without local physical observations other than loud borborygmi would lend tenable and substantial support to the impression that an obstruction exists.

Normally, gas is visible on the x-ray film in the stomach and colon, especially at the hepatic and splenic flexures, but cannot be visualized

Fig. 8.—Roentgenogram of the abdomen of a woman who had complained of intermittent colicky pain for seven hours. There is gaseous distention of a small loop of small intestine on the left side of the abdomen. Loud intestinal noises on auscultation were the only physical observation. An adhesive band was found at operation.

through the length of the small intestine. That gas is present in the small intestine is well known. Every surgeon is familiar with the small bubbles of intestinal fluid and air that escape when the normal intestine is incised. The intimate intermixture of gas and fluid probably precludes the gas being distinguished normally from the immediate

surroundings. The air that is swallowed during the ingestion of food remains for a time in the stomach as the large gaseous "stomach bubble," and in the digestive processes that continue in the small intestine, carbon dioxide largely is formed and is absorbed almost as readily. Normally, protein putrefaction begins in the large intestine; as a product of this bacterial activity, nitrogen, hydrogen, methane and hydrogen sulphide are formed, which are absorbed much less readily than carbon dioxide. At the same time, it is to be remembered that the transit of food through

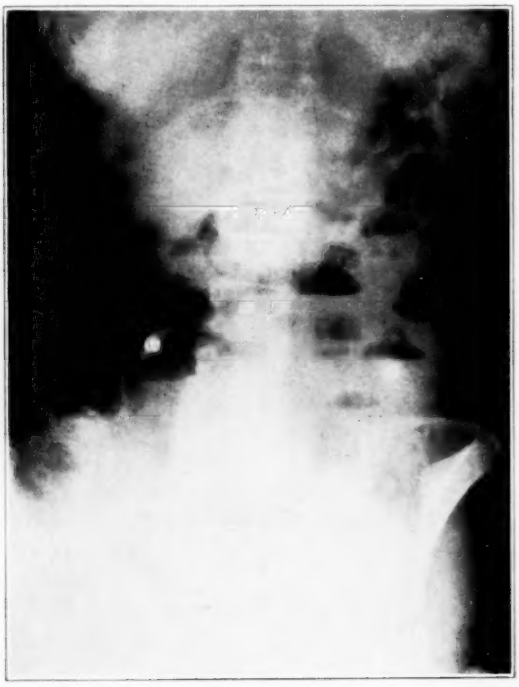

Fig. 9.—Roentgenogram made in standing posture showing "fluid mirrors." The patient had had obstructive symptoms of twelve hours' duration. No clinical distention, loud borborygami and a metallic tinkle were the only physical observations.

the small intestine is rapid. In the stomach and in the colon progress of the content of the digestive tract is considerably slower.

The demonstration of gas in the small intestine on the x-ray film is therefore decidedly abnormal and is indicative of the presence of a mechanism interfering with the normal rate of transit through the small intestine. It is to be remembered, however, that this mechanism

may be mechanical or inhibitive. In inhibition or paralytic ileus of peritonitis, the stethoscope will reveal a relatively silent abdomen. When the plate is taken in the erect posture, "fluid mirrors" can be made out —concrete evidence of the collection of fluid and gas, affording definite proof of the presence of intestinal stasis.

Lynch and one of us (O. H. W.)[4] recently put this roentgen evidence of intestinal obstruction to experimental test in the dog. Within four or five hours after the obstruction, definite dilatation of the coils of intestine proximal to the site of intestinal interruption was noted.

In acute intestinal obstruction the administration of barium sulphate is of little help in making an early diagnosis, except in obstructions of the colon or stomach outlet.

Alterations in the blood chemistry are significant of a block high in the intestine but afford no early evidence of intestinal obstruction.

In summarizing briefly the criteria on which an early diagnosis of simple obstruction can be made, it may be said: In a patient complaining of intermittent colicky pain in whom vomiting is usually a prominent feature, but who presents no local physical observations, intestinal obstruction is strongly to be considered. Loud intestinal noises of a metallic character elicited on auscultation of the abdomen lend tenable support to such an impression. The detection of gaseous shadows in the small intestine in the x-ray film adds confirmation and establishes the diagnosis. The continuation of pain despite the return of gas and feces with an enema is indication for immediate operation.

CONCLUSION

The bowel distal to the point of obstruction responds to the injection of enemas much as does the normal intestine. The ability to expel gas and fecal material following the administration of an enema does not militate against the presence of intestinal obstruction.

4. Wangensteen, O. H., and Lynch, F. W.: Evaluation of X-Ray Evidence as Criteria of Intestinal Obstruction, Proc. Soc. Exper. Med. & Biol. **27**:674 (April) 1930.

PRIMARY CARCINOMA OF THE LUNGS WITH METASTASES TO THE CENTRAL NERVOUS SYSTEM *

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Metastases of primary carcinoma of the lung to the central nervous system and other organs are not infrequent. Simpson,[1] in a collection of 139 cases of patients who were admitted to the London Hospital between 1907 and 1925, and in whom primary carcinoma of the lung was found post mortem, stated that metastases were noted during life in about 25 per cent of the cases. Adler,[2] in a collection of 327 cases, found only 33 cases in which there were no metastases. Frequently the metastases constitute the first sign of the disease, producing symptoms and signs in the organ involved, without any evidence of the primary site of the growth, thus leading to errors in diagnosis. Simpson,[1] in the analysis of his cases, found 66 in which the condition was diagnosed incorrectly, and of these 18 were placed in the domain of diseases of the central nervous system (13 in the cerebral group and 5 in the spinal group). Dosquet,[3] in 105 cases of carcinoma of the lungs found involvement of the central nervous system in 31.4 per cent. Fried,[4] in a collection of 10 cases, found metatases to the central nervous system in 4, and in 1 of the cases the signs and symptoms led to a clinical diagnosis of alcoholic psychosis. The condition in only 3 of the 10 cases reported was diagnosed clinically as primary pulmonary carcinoma. Parker[5] reported 4 cases of primary carcinoma of the lung with invasion of the brain, meninges, spine and nerve roots, in which the pulmonary signs were few and the involvement of the nervous system was the most striking feature.

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*Submitted for publication, March 5, 1930.

*From the Neuropathology Laboratory, Montefiore Hospital.

1. Simpson, S. L.: Primary Carcinoma of the Lung, Quart. J. Med. **87**:413 (April) 1929.

2. Adler, I.: Primary Malignant Growth of the Lungs and Bronchi, New York, Longmans, Green & Company, 1912.

3. Dosquet, quoted by Parker (footnote 5).

4. Fried, B. M.: Primary Carcinoma of the Lungs, Arch. Int. Med. **35**:1 (Jan.) 1925.

5. Parker, H. L.: Involvement of the Central Nervous System Secondary to Primary Carcinoma of the Lungs, Arch. Neurol. & Psychiat. **17**:198 (Feb.) 1927.

Metastases to the brain are considered to take place by two routes, (1) through the blood stream, the tumor cells being carried by the pulmonary veins to the left side of the heart and thence by the general circulation to the central nervous system, and (2) by direct extension through the cervical lymph glands and the lymphatic spaces of the neck. According to Hassin,[6] the tumor cells may be carried from the lymph glands of the neck by a backward flow of the lymph through the perineural sheath to the subdural and subarachnoid spaces, and then to the cerebral meninges. The first method of invasion is the more common.

A series of cases of primary carcinoma of the lungs with involvement of the central nervous system presenting some interesting features induced us to investigate this problem.

MATERIAL

This work covers the investigation of 109 cases with a clinical diagnosis of primary carcinoma of the lung at the Montefiore Hospital since 1922. Of these, 61 cases came to autopsy, and the condition was proved to be primary carcinoma of the lungs. Twelve of the total number of cases presented involvement of the central nervous system, chiefly in the form of cerebral and cerebellar metastases, with only 3 cases showing pure metastases to the spinal cord in the form of transverse myelitis. The brains and spinal cords were obtained in only 7 of the 12 cases. The cases showing involvement of the central nervous system were divided in two groups: (1) those of primary carcinoma of the lungs with involvement of the central nervous system by metastases in which the brains and spinal cords were removed (table 1) and (2) those of primary carcinoma of the lungs showing clinically involvement of the nervous system in which the brains and spinal cords were not obtained at autopsy (table 2).

REPORT OF CASES

Group 1.—Cases of Primary Carcinoma of the Lungs with Involvement of the Central Nervous System by Metastases in Which the Brains and Spinal Cords Were Removed (Table 1).

Case 1.—*History.*—M. C., a man, aged 70, a presser, was admitted to the Montefiore Hospital on March 20, 1922. On account of the patient's mental condition, a satisfactory history could not be obtained.

Physical Examination.—Examination revealed a pale, anemic, emaciated man who presented a palpable and painful mass in the left infraclavicular fossa. The chest showed dulness of both apexes posteriorly, flatness of the left infraclavicular fossa and bronchial breathing. The heart and the rest of the organs were normal.

6. Hassin, G. B.: Histopathology of Carcinoma of the Cerebral Meninges, Arch. Neurol. & Psychiat. **1**:705 (June) 1919.

Neurologic Examination.—The pupils were irregular and reacted slowly to light; the fundi revealed optic atrophy. There was a slight right facial palsy. The patient was in the hospital only four days when he died suddenly on March 25, 1922. A diagnosis of neoplasm involving the left lung, the wall of the chest and the second rib was made.

TABLE 1.—*Observations on Cases of Primary Carcinoma of the Lungs with Involvement of the Central Nervous System by Metastases in Which the Brains and Spinal Cords Were Removed*

Case, Sex, Age	Duration of Illness, Years	Onset of		Clinical Diagnosis	Clinical Neurologic Signs Due to Metastases	Observations at Autopsy	Involvement of Central Nervous System, Single or Multiple	Histogenesis of Tumor
		Pulmonary Signs	Neurologic Signs					
1 M 70	?	Sudden	Sudden	Carcinoma of lungs	Optic atrophy facial palsy	Carcinoma of lungs with metastases to brain and various organs	Single	Bronchial
2 M 64	9	Gradual	Sudden	Carcinoma of lungs with cerebral metastases	Aphasia; left hemiplegia	Carcinoma of lungs with metastases to brain and various organs	Single	Bronchial
3 F 34	6	Gradual	Sudden	Carcinoma of lungs; chronic pulmonary tuberculosis; tuberculoma or tuberculous meningitis	Papilledema; Kernig's sign; exaggerated reflexes	Carcinoma of lungs with metastases to brain and various organs	Multiple	Bronchial
4 F 40	1½	Sudden	Sudden	Gumma; bronchopneumonia; dementia paralytica; possibility of cerebral neoplasm	Argyll-Robertson pupils; choked disk; mental picture of dementia paralytica	Carcinoma of lungs with metastases to lymph nodes of the hilus and brain	Single	Bronchial
5 F 58	1	Sudden	Sudden	Chronic fibroid phthisis; generalized arteriosclerosis	Headache; tinnitus	Carcinoma of lungs with metastases to brain and various organs	Multiple	Bronchial
6 M 50	1	Sudden	Sudden	Carcinoma of lungs	Headache; dizziness	Carcinoma of lungs with metastases to brain and various organs	Multiple	Bronchial
7 M 61	2	Gradual	Sudden	Chronic pulmonary tuberculosis; compression of spinal cord	Signs of spinal cord tumor; level lesion	Carcinoma of lungs with metastases to various organs and vertebral column	Single	Bronchial

Laboratory Data.—A roentgenogram showed a dense circumscribed homogeneous shadow occupying nearly the entire upper lobe of the left lung. The ninth rib on the right side showed a partial destruction of its posterior portion. The Wassermann test of the blood was negative.

Anatomic Diagnosis.—The condition was diagnosed neoplasm of the left lung with extension through the first intercostal space and partial erosion of the second rib with metastases to the ribs, suprarenal gland and brain; generalized arteriosclerosis, and terminal bronchopneumonia.

Autopsy Observation on the Brain.—The brain showed a slight edema over the parietal region. A large tumor nodule 3 cm. in diameter was found immediately underneath the occipital angle, breaking through the cortex on the left side. The vessels at the base were slightly thickened. On sectioning the brain, a tumor mass was found located in the left parieto-occipital area.

Microscopic Report on the Metastatic Nodule to the Brain.—The tumor cells, squamous in type, were large, deeply staining, polygonal, round and flattened, containing distinct round vesicular nuclei. In places, the cells were pale with large nuclei and strikingly prominent nucleoli (fig. 1). For the most part a thin connective tissue stroma acted as the supporting framework for individual and several layers of cells. In places there was a tendency to alveolar formations,

TABLE 2.—*Observations on Cases of Primary Carcinoma of the Lungs Showing Clinical Involvement of the Nervous System by Metastasis in Which the Brains and Spinal Cords Were Not Obtained at Autopsy*

Case, Sex, Age	Duration of Illness, Months	Onset of: Pulmonary signs	Onset of: Neurologic signs	Clinical Diagnosis	Clinical Neurologic Signs Due to Metastases	Observations at Autopsy	Comment
1 M 48	2	Sudden	Sudden	Carcinoma of lungs	Babinski sign; stupor; incontinence	No postmortem examination	Brain and cord not removed
2 M 46	24	Sudden	Sudden	Carcinoma of lungs with metastases to the spine	Horner's syndrome; lesion at level of D-4-5	No postmortem examination	Brain and cord not removed
3 M 47	13	Sudden	Sudden	Carcinoma of lungs; pulmonary tuberculosis	Multiple neurologic signs, chiefly of the bulb	No postmortem examination; primary carcinoma of the lungs	Brain and cord not removed; patient died at home
4 F 56	12	Gradual	Gradual	Carcinoma of lungs; chronic encephalitis; cerebral metastasis	Chronic encephalitis; left hemiplegia; aphasia; convulsions	Carcinoma of lungs	Brain and cord not removed
5 M 53	11	Sudden	Sudden	Carcinoma of lungs with metastasis to spine	Transverse lesion at D-8	Carcinoma of lungs	Brain and cord not removed

and in the necrotic areas tumor cells were found invading the walls of the blood vessels (fig. 2).

Microscopic Diagnosis.—The microscopic diagnosis was carcinoma simplex (bronchial in origin).

Comment.—The short stay of this patient in the hospital and the poor history obtained owing to the patient's mental condition rendered this case unsatisfactory for diagnosis. The interesting features were the palpable masses in the infraclavicular fossa and the solitary tumor nodule invading the brain tissue. The involvement of the glands of the neck and the solitary metastatic nodule to the brain are in favor of a direct extension of the mass from the cervical lymph glands and the lymphatic spaces of the neck by a backward flow of the lymph.

Case 2.—*History.*—A. L., a man, aged 64, a salesman, was admitted to the hospital on Nov. 22, 1926. About September, 1923, the patient complained of pain in both flanks and loss in weight. In July, 1926, he sustained a fall and bruised his head; this was followed by a paralysis of the right arm. Six days later, he fell again. A left facial palsy, stuttering and incontinence of both sphincters developed. He fell out of bed and was semiconscious for two weeks, following which left hemiplegia and marked aphasia developed. For the nine

Fig. 1.—Metastatic carcinoma simplex, bronchial in origin, showing pale cells with large, vesicular nuclei and others with strikingly pyknotic nuclei; hematoxylin and eosin stain; × 300.

years before admission he had coughed, bringing up considerable thick, yellowish sputum.

Physical Examination.—Examination revealed a markedly emaciated, cachectic man with the mouth drawn to the left. The right side of the chest expanded poorly. There was an area of dulness on the right side anteriorly from the third to the fifth ribs and posteriorly from the fifth interspace to the angle

of the scapula, with tubular breathing which was heard over this entire area. The left lung, as well as the rest of the organs, was negative.

Neurologic Examination.—The pupils were the size of a pin-point and reacted slightly to light. There was a right lower facial palsy. The tongue deviated to the right. All extremities were flaccid, with marked atrophy of the muscles of the lower extremities. Sensation was unsatisfactory, as the patient cooperated poorly. The reflexes of the upper extremities were normal. Both

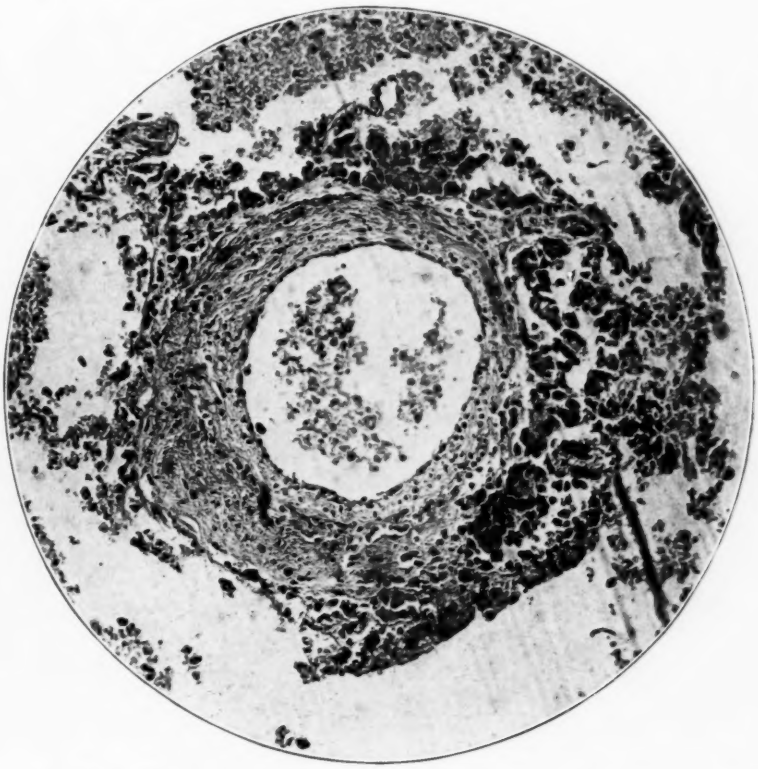

Fig. 2.—Blood vessels invaded and surrounded by tumor cells; hematoxylin and eosin stain; × 400.

knee jerks were diminished, but the ankle jerks were present. There was a positive Babinski sign on the right. The patient was aphasic, chiefly on the emissive side.

Laboratory Data.—Examinations of the spinal fluid and the Wassermann reaction were negative. The blood picture presented a slight secondary anemia. The blood pressure was 100 systolic and 70 diastolic. The sputum was negative for tubercle bacilli. Roentgen examination of the left side of the chest showed a large mass in the superior mediastinum, the size of an apple. The edges were

sharply delineated, but along its external aspect there were a few infiltrating bands. Roentgenograms of the lumbar and dorsal spine were negative. Examination was suggestive of a neoplasm.

The patient died on Dec. 17, 1926.

Diagnosis.—The clinical diagnosis was carcinoma of the lung with metastases and left internal capsular hemorrhage due to metastases. The anatomic diagnosis was carcinoma of the left lung with metastases to the left suprarenal gland and brain with extension into the pancreas and left kidney; fibroma of the dura, generalized arteriosclerosis and terminal vegetative endocarditis.

Fig. 3.—Metastatic nodule to the frontal area.

Autopsy Observations on the Brain.—The gyri were swollen and flattened, and the left hemisphere was enlarged. On cutting the brain vertically, a tumor-like mass was found in the left hemisphere extending frontally into the precentral gyrus (fig. 3) and caudally into the interior third of the middle parietal gyrus. The tumor was reddish. The rest of the central nervous system revealed no abnormalities.

The microscopic examination of the metastatic nodule of the brain showed the same histologic features as the primary tumor with extensive degeneration of the nervous tissue (fig. 4). A descending degeneration of the left pyramidal tract was found in the pons, medulla oblongata and the lower cervical segments of the cord. This tumor presented a single cerebral metastasis.

Comment.—The cerebral symptoms in this case came on suddenly with a fall, which undoubtedly was secondary (i. e., the fall) to the lesion in the brain. The age of the patient could easily have led one to make a diagnosis of cerebral hemorrhage. The careful examination of the chest and the roentgenogram of the chest prevented an error in the neurologic diagnosis.

Fig. 4.—Metastatic papillary adenocarcinoma of the brain showing slight necrosis; hematoxylin and eosin stain; × 300.

CASE 3.—*History.*—R. G., a woman, aged 34, a housewife, was admitted to the hospital on Jan. 11, 1928. In October, 1927, the patient caught cold. She had a temperature of from 100 to 101 F. for ten days, followed by cough, blood-streaked sputum and loss in weight. Dysphagia, pain in the throat and vomiting were present for eight weeks before admission. The past history was negative, except for a tracheotomy at the age of 5 following laryngeal diphtheria and a persistent cough and expectoration for six years.

Physical Examination.—Examination revealed a well developed and well nourished woman. There was limitation in motion of the right side of the chest, flatness anteriorly between the fourth and tenth ribs and posteriorly between the third and tenth ribs and absent vocal fremitus over the same area. Above these areas there was bronchial breathing. The other organs were normal, with the exception of a movable mass palpated in the right side of the abdomen. A hydropneumothorax in the right side of the chest with a tumor mass in the lower part of the right lung was considered.

Neurologic Examination.—There was exaggeration of the deep reflexes of all the extremities, with a twitching of the left hand. On March 26, 1928, a left hemiparesis, a papilledema of 2 diopters with retinal hemorrhages out of proportion to the amount of elevation and a bilateral Kernig sign with rigidity of the neck developed.

Laboratory Data.—The sputum was positive for tubercle bacilli on two or three occasions. A roentgenogram showed a dense shadow in the right side from the apex to the diaphragm, probably due to pleural thickening and pleural effusion. Examination of the skull gave negative results. The blood count showed red blood cells, 2,100,000; white blood cells, 9,800; hemoglobin, 65 per cent. The differential count was normal. The spinal fluid showed 40 cells and a slight amount of globulin. The cells were mononuclear. The Wassermann tests of the blood and spinal fluid were negative.

Diagnosis.—The clinical diagnosis was primary carcinoma of the lung superimposed on an old fibroid tuberculosis. The neurologic diagnosis was tuberculoma or tuberculous meningitis. The possibility of a metastatic neoplasm was considered. The anatomic diagnosis was papillary adenocarcinoma of the right lung with extension to the pleura and lymph nodes; metastases to the left lung, kidneys, suprarenals, retroperitoneal lymph nodes, liver and brain and uterine fibroids.

Autopsy Observations on the Brain.—The right hemisphere was larger than the left, with flattening of the gyri and sulci. When the brain was cut vertically in the anteroposterior direction, a marked swelling of the whole right hemisphere was found. At the tip of the right caudate nucleus, there was a small tumor mass measuring approximately 0.5 cm. in diameter. In the right upper parieto-occipital region (fig. 5), there was a large globular mass measuring 2 cm. in diameter extending to the outer surface and breaking through into the meninges. The center of the tumor was yellowish and necrotic. The rest of the central nervous system was free from metastases. Sections of the metastatic nodule to the brain at about the tip of the caudate nucleus consisted of alveolar masses lined by columnar type of cells. Between the glandular elements (fig. 6) there was a stroma of dense connective tissue, as well as a dense accumulation of apparent round cell infiltration in the necrotic areas. Some of the tumor cells had definite mitotic figures. The microscopic diagnosis was metastatic adenocarcinoma of the brain (bronchial in origin).

Comment.—This case showed a gradual onset of the pulmonary symptoms with a sputum positive for tubercle bacilli on several occasions. A diagnosis of neoplasm of the lung superimposed on an old fibroid tuberculosis was considered. The neurologic signs came on rather late and suddenly about one month prior to death, the diagnosis being tuberculoma, tuberculous meningitis or metastatic neoplasm. The

bilateral Kernig sign, the rigidity of the neck and the sputum positive for tuberculosis led to a consideration of tuberculous meningitis. The metastases to the central nervous system were multiple. The histologic picture was that of an adenocarcinoma of the lung originating from the cells of the bronchus.

Case 4.—*History.*—E. T., a woman, aged 40, an actress, was admitted to the hospital on Sept. 11, 1928, with a complaint of general weakness, irritability and incontinence of the spinchters. The patient, who had always been quarrelsome, became irritable in August, 1927. In a few months she began to cough, lost weight and became incontinent. In June, 1928, she became violent, and was sent to a state

Fig. 5.—Metastatic nodule of the right parieto-occipital region.

institution, where a diagnosis of dementia paralytica was made. Here she received five injections of arsphenamine. At this institution numerous râles were heard over both lower lobes posteriorly. The condition became worse, and later considerable consolidation of the left lower lobe of the left lung was noticed, with bronchial breathing and a moderate amount of fluid in the right side of the chest.

One brother had died of dementia paralytica, and one brother was being treated at the time for syphilis. She had been married for seven years and was separated from her husband. There had been no pregnancies or miscarriages.

Physical Examination.—Examination showed a fairly well developed but poorly nourished woman. The right cervical glands were palpable in the supraclavicular region. A gland the size of a walnut, firm, somewhat irregular and adherent to its bed was palpated in the anterior triangle of the neck. The lungs showed diminished resonance over the right apex and flatness in the right axilla

posteriorly and anteriorly. Breath sounds were absent from the third interspace to the apex, and there were numerous moist râles. The left lung showed bronchial breathing at the base, with moist gurgling râles.

Neurologic Examination.—The patient was uncooperative and irritable and was disoriented as to time, place and person. Memory was poor for recent and remote events. Judgment was poor. She had some insight into her condition. There were no delusions, illusions or hallucinations. The positive neurologic obser-

Fig. 6.—Metastatic adenocarcinoma to the brain; hematoxylin and eosin stain; ×300.

vations were: The pupils did not react to light or in accommodation; they were irregular and slightly unequal. The fundi showed bilateral choked disk. There was a general hyperreflexia, a bilateral Hoffmann sign, exhaustible ankle clonus and absent abdominal reflexes on the right, coarse tremor of both hands and tongue, difficulty in recognizing objects with the left hand and a suggestion of right finger-to-nose-ataxia.

Laboratory Data.—A roentgenogram of the chest showed small, scattered areas of consolidation throughout all the lobes, suggesting bronchopneumonia. Examination of the skull gave negative results. The spinal fluid showed a positive albumin and globulin content and 40 cells. The Wassermann test of the spinal fluid was negative; that of the blood was four plus.

Death occurred on Oct. 1, 1928.

Diagnosis.—The clinical diagnosis was possible cerebral neoplasm, dementia paralytica and bronchopneumonia. The anatomic diagnosis was carcinoma of the lung, metastases to the lymph nodes of the hilus, brain and pancreas and bronchopneumonia. The microscopic diagnosis was primary papillary carcinoma of the lungs.

Autopsy Observations on the Brain.—The brain was normal in appearance. There were no masses in any areas of the brain, with the exception of an encapsulated mass in the region of the right cerebellum, a little larger than a hazelnut (fig. 7). A piece of tissue from the encapsulated mass of the cerebellum showed it to consist of a conglomeration of epithelial cells much like the arrangement of the epithelial cells of the alveolar tissue in the lungs (fig. 8). Numerous mitotic figures were observed.

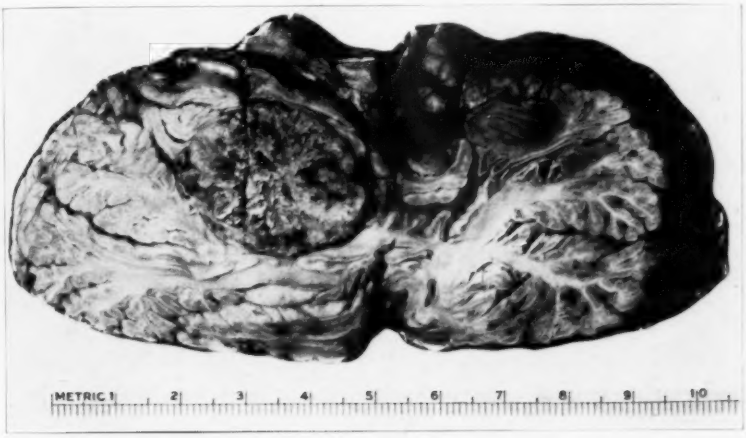

Fig. 7.—Metastatic nodule of the left lobe of the cerebellum.

Sections of the brain were made from various areas and showed a slight thickening of the meninges with a collection of inflammatory cells. The brain tissue proper showed a disturbance of the architectural layers with slight perivascular infiltration within the vessels. There was some proliferation of the capillaries. Numerous rod cells were found. The nerve cells showed various changes, from shrinkage to complete destruction.

The microscopic diagnosis was metastatic carcinoma of the cerebellum (primary, carcinoma of the lung).

The neuropathologic diagnosis was metastatic carcinoma of lung to the cerebellum; dementia paralytica.

Comment.—The cerebral symptoms predominated in this case. The Argyll Robertson pupils, the history of a positive Wassermann reaction of the blood and the mental condition pointed to dementia paralytica, but the negative Wassermann test of the spinal fluid militated strongly against such a diagnosis. The presence of choked disk is almost unknown in dementia paralytica. This observation, with the suspicion

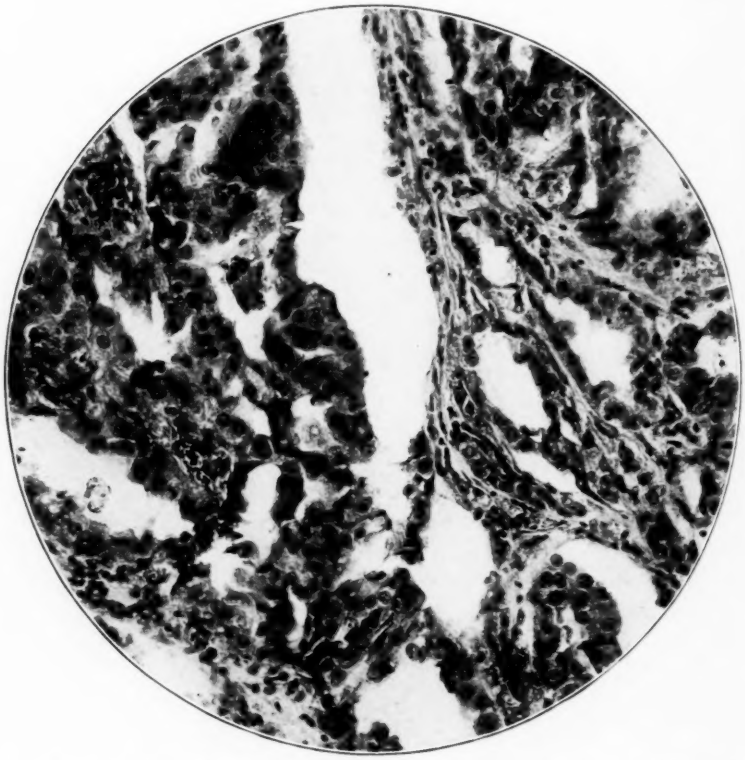

Fig. 8.—Metastatic papillary adenocarcinoma of the cerebellum; hematoxylin and eosin stain; × 300.

of a left-sided impairment of stereognosis, led to the consideration of a cerebral neoplasm located in the parietal region. The only cerebellar sign was a suggestion of the finger-to-nose ataxia. Tumors of the posterior fossa have been described which give a mental picture similar to the one seen in tumors or neoplasm of the frontal lobe. The conjoint histopathologic observations of dementia paralytica and a cerebellar tumor easily explain the difficulty in the diagnosis. The obser-

vations on the chest were not interpreted, although a co-existent bronchopneumonia (which was probably terminal) superimposed on the new growth was found. There was evidence of involvement of the cervical lymph glands with a metastasis to the cerebellum.

CASE 5.—*History.*—S. L. a woman, aged 58, was admitted to the hospital on April 5, 1929. One year before admission the patient was troubled by a chronic cough accompanied by headache and tinnitus. In March, 1928, she had choking spells lasting from three to five minutes, during which period she became dyspneic. She later expectorated blood-streaked sputum. A diagnosis of pulmonary tuberculosis was made.

Physical Examination.—Examination showed a white woman, acutely ill, cyanotic, dyspneic and apprehensive. The pupils were unequal, the right being greater than the left, and regular and reacting promptly to light and in accommodation. Examination of the lungs was rather unsatisfactory on account of the patient's critical condition. The right lung showed flatness of the apex with hyperresonance below the clavicle. The left lung showed impaired resonance. Numerous moist, high-pitched râles were heard over the entire chest. Diffuse precordial pulsations were noticed.

Diagnosis.—The diagnosis was chronic fibroid phthisis, generalized arteriosclerosis, cardiac hypertrophy and dilatation and hypertension. The blood pressure was 194 systolic and 90 diastolic.

The patient died five and one half hours after admission.

The anatomic diagnosis was carcinoma of the bronchus with metastases to the lungs, pericardium, heart, tracheobronchial lymph glands, thyroid, liver, spleen, suprarenals, pancreas, ribs, skull, dura and pituitary; hydropericardium and multiple hemangiomas of the liver.

Autopsy Observations on the Brain.—The pia-arachnoid had a glistening appearance. The vessels were prominent, especially over the right rolandic and sylvian fissures. In the right prerolandic region there was a hemorrhagic encapsulated mass (fig. 9) with slight narrowing of the ventricle on that side Additional nodules were found in the region of the diencephalon, globus pallidus, left caudate nucleus and in the pons. A few masses were found in both lobes of the cerebellum (fig. 10).

The histologic picture of the metastases to the brain showed a similar appearance to the original tumor mass. The microscopic diagnosis was metastatic papillary adenocarcinoma.

Comment.—This patient was in the hospital only five and one-half hours. A diagnosis of pulmonary tuberculosis was made. The interesting feature of this case was the metastasis to the heart muscle, a structure rarely involved by new growths. The involvement of the central nervous system was in the form of multiple metastases with a hemorrhage in the prerolandic area.

CASE 6.—*History.*—I. S., a man, aged 50, a merchant, was admitted to the hospital on Sept. 29, 1928, with the complaint of cough, hemoptysis and weakness which he had noticed for one year.

Physical Examination.—The right lung showed dulness anteriorly from the fourth interspace down and posteriorly from the seventh interspace to the base and axillary region. The breath sounds over these areas were diminished. Râles

were heard over the anterior and infraclavicular regions. The left lung showed no abnormalities. There was moderate clubbing of the fingers. The heart and abdomen were normal.

Neurologic Examination.—The right pupil was larger than the left; both reacted to light and in accommodation. All deep reflexes were hyperactive but equal. Other neurologic observations were negative.

Course.—The patient received deep roentgen treatments. He did well until May 11, 1929, when he fell and lacerated his scalp while attempting to get out of bed. Thereafter he began to complain of headaches and dizziness. There were no

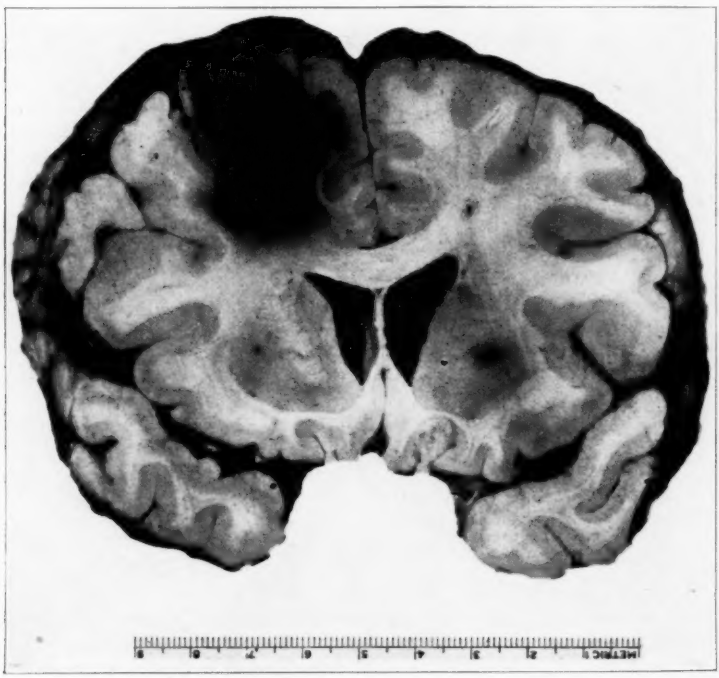

Fig. 9.—Hemorrhagic encapsulated mass in the prerolandic area with two small nodules located in the left corona radiata and caudate nucleus.

signs of fracture of the skull. A neurologic examination at this time showed nothing of note. The day before death (May 15, 1929) a temperature of 105 F. suddenly developed with signs of bronchopneumonia in the right lung.

Laboratory Data.—A roentgenogram of the chest showed numerous small calcified infiltrations in the upper lobe of the right lung and in the lower lobe partial consolidation which was suggestive of a neoplasm. Other laboratory examinations gave negative results.

Diagnosis.—The clinical diagnosis was primary carcinoma of the right lung. The anatomic diagnosis was carcinoma of the lung with metastases to the

abdominal lymph nodes, spleen and cerebellum with necrosis; bronchiectasis of the right lung and bronchopneumonia.

Autopsy Observations on the Brain.—The vessels of the brain were markedly congested, especially over the right hemisphere. A slight area of softening involving the tip of the left occipital lobe and left lobe of the cerebellum was noted. On sectioning the brain vertically, the anterior horns of the lateral ventricles were symmetrically enlarged. In the region of the pons on the right side, a gelatinous tumor mass was found which involved the substantia nigra and the pontile fibers (fig. 11). This gelatinous tumor mass was hemorrhagic at the upper and outer borders. Another mass was found involving part of the right cerebellum as well as the vermis (fig. 12). A cavity containing necrotic material was found involving practically the whole side of the left cerebellum.

Sections of the tumor masses in the central nervous system presented the same histologic features as those found in the lung.

Fig. 10.—Numerous small metastatic nodules to the cerebellum.

Diagnosis.—The condition was diagnosed metastatic adenocarcinoma.

Comment.—The neurologic symptoms came on suddenly about four days prior to death without definite localizing signs. The pulmonary signs antedated the neurologic signs by one year. The histogenesis of the tumor was that of an adenocarcinoma of bronchial origin.

Case 7.—*History.*—S. B., a man, aged 61, a jeweler, was admitted to the hospital on July 27, 1929, with the complaints of pain in the back radiating to the left upper extremity, loss of motion in the lower extremities and cough. The patient had had a chronic productive cough for the last thirty to forty years; the expectoration became profuse and blood-streaked eighteen months before admission. In September, 1927, he woke up one morning with intense pain and stiffness of the extremities aggravated by movements of the neck. In May, 1929, he was confined to bed, as he was unable to stand or walk. He noticed paresthesias of the left hand and forearm and frequency in micturition.

Physical Examination.—The patient was markedly emaciated. The trachea was displaced to the right. There was drooping of the right shoulder. The right supraclavicular and infraclavicular fossae were deeper than the left. There was lagging of the left side of the chest, flatness of both apexes and cavernous breathing. All other organs were normal.

Neurologic Examination.—There was complete immobility of the neck. The left pupil was irregular, and both pupils reacted sluggishly to light. There was a left Horner's syndrome with complete paralysis of the left lower extremities and

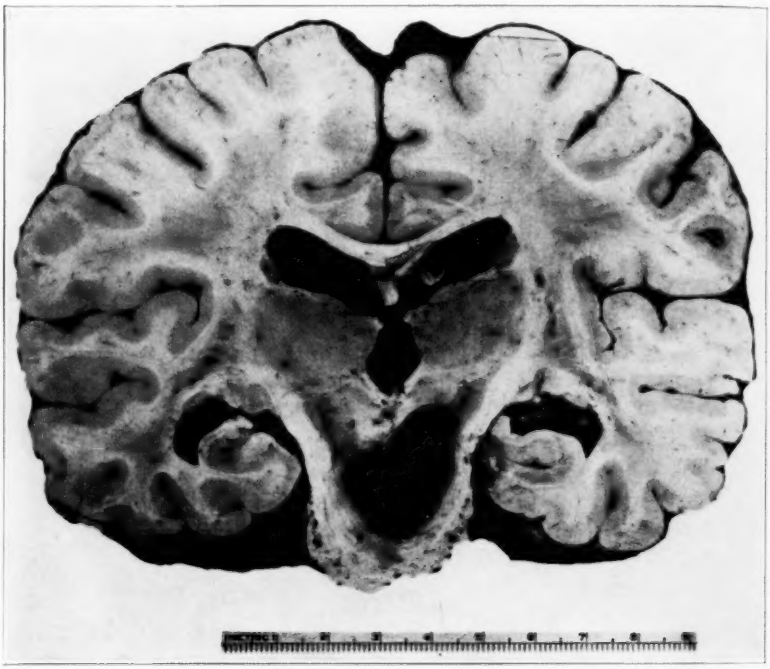

Fig. 11.—Metastatic tumor of the pons involving the pes pedunculi and substantia nigra.

paresis of the right lower extremities. All the deep reflexes were markedly diminished, the left more than the right. There was wasting of the thenar, hypothenar and interossei muscles, more marked on the left. Sensation showed a belt of hyperalgesia at the third dorsal vertebra, below which level all forms of sensibility were either diminished or lost. The paralysis was flaccid.

Course.—Later a bilateral foot drop, flexion of the right lower extremity and a marked cystitis developed, and the patient died on July 21, 1929.

Laboratory Data.—A roentgenogram of the thoracic spine disclosed a moderate degree of spondylitis, but no definite evidence of Pott's disease. The upper lobe of the left lung revealed a shadow extending from the apex to the fifth rib poste-

riorly. The trachea showed displacement to the right. No definite statement could be made in regard to the state of the first, second and third dorsal vertebrae. The spinal fluid showed xanthochromia, 4 plus albumin and globulin and 4 lymphocytes, with evidence of partial block. The urine became loaded with pus cells before death.

Diagnosis.—The condition was diagnosed clinically as chronic bilateral fibroid tuberculosis, carcinoma of the left lung with metastases, compression myelitis of the spinal cord and chronic cystitis and pyelitis. The anatomic diagnosis was primary carcinoma of the lung with metastases to the vertebrae and liver.

Autopsy Observations on the Spinal Cord.—A small portion of the cord, to which a mass was attached, was removed from the upper dorsal region. On sectioning, the cord was seen to be distorted.

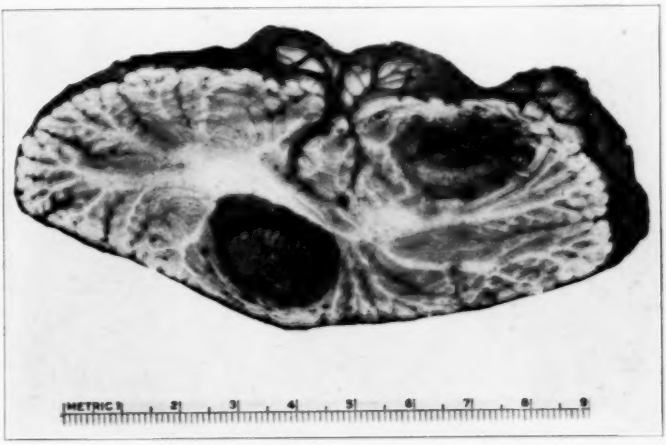

Fig. 12.—Metastatic tumor nodules to both lobes of the cerebellum.

Frozen and celloidin sections of the spinal cord were stained by the modified Loyez, hematoxylin and eosin, Mallory phosphotungstic, van Gieson, sudan IV, Cajal and Bielschowsky methods. The sections at the second dorsal vertebra with the modified Loyez method showed the outline of the cord to be markedly distorted with a tumor mass situated extradurally along the lateral surface of the cord (fig. 13). The vertical diameter was greater than the lateral diameter, the reverse of what is usually seen in the normal cord at this level. Under higher power magnification, there was no evidence of marked demyelination of the white fibers. With the cellular stains the anterior horn cells had undergone various changes, from disappearance of the Nissl substance to complete destruction. There were no evidences of compound granular corpuscles as seen in areas of softenings. With the glia stains, the glial elements did not show any changes. The blood vessels in the pia-arachnoid and within the cord were normal and did not show any signs of occlusion by the extradural mass.

With the Bielschowsky stain, the axis cylinders were fairly well preserved. Occasional axis cylinders showing swelling and corkscrew appearance were seen.

Sections below the level of the compression did not show any signs of descending demyelination. At the fifth and sixth dorsal vertebrae there was marked widening of the anterior spinal fissure with some destruction of the gray matter.

The tumor consisted of numerous fibroblasts which in places had a definite whorl formation. Between the fibroblasts numerous polyhedral-shaped cells with deeply stained, irregular nuclei were found. In places, these cells had a definite acinar arrangement; in others, they were densely grouped together. The dura was markedly thickened and invaded by the tumor cells. A few spicules of bone were found within the tumor tissue, probably from the breaking down of the vertebrae. The general appearance of the tumor, with the exception of the thickened dura, resembled the primary neoplasm in the lung which was bronchial in origin.

Fig. 13.—Extramedullary compression of the spinal cord by tumor mass causing distortion of the cord without marked degeneration of the white matter; Weil stain; × 10.

Comment.—The condition in this case was considered as chronic pulmonary tuberculosis, although a neoplasm was thought of. This is the only case posted which disclosed a metastatic nodule to the cord causing its compression. Metastases to the vertebrae or cord are not so common as those found elsewhere in the central nervous system. The cord in this case did not show evidences of softening, as in some cases of compression in which the circulation of the cord is frequently interfered with.

Group 2.—Cases of Primary Carcinoma of the Lungs Showing Clinically Involvement of the Nervous System by Metastases in the Brains and Spinal Cords Which Were not Secured at Autopsy (Table 2).

Case 1.—*History.*—M. D., a man, aged 48, a milkman, was admitted to the hospital on Dec. 19, 1923, complaining of pain in the right side of the chest, the right calf and the back of the neck for the past three weeks. In October, 1923, the patient caught cold, following which a severe cough and pain developed on the right side. He noticed difficulty in starting to urinate and later had to be catheterized. At this time, he noticed pain in the right calf and began to lose weight.

Physical Examination.—Examination showed an emaciated man with a generalized wasting over the entire body. There was lagging of the chest on the right side, with flatness on percussion posteriorly. Occasional moist, crackling râles were heard over the same area. The breath sounds were barely perceptible posteriorly. The blood pressure was 110 systolic and 80 diastolic.

Neurologic Examination.—The pupils were small and equal and reacted well to all stimuli. The upper reflexes were moderately increased, with a suggestive Babinski sign on the left. The patient was unable to use the left leg and was incontinent. He died Jan. 23, 1924.

Laboratory Data.—On roentgen examination a large mass was seen extending from the hilus at the level of the sixth to the tenth ribs infiltrating the pulmonary tissue. Other laboratory examinations gave negative results.

Diagnosis.—The diagnosis was carcinoma of the lower lobe of the right lung.

Comment.—The neurologic signs were rather indefinite, and cerebral or spinal cord localization was difficult. A possibility of both spinal cord and cerebellar involvement was most likely. Autopsy was not performed.

Case 2.—*History.*—N. B., a man, aged 46, an employment agent, was admitted to the hospital on Feb. 6, 1926, with pain in the right side of the chest of fourteen months' duration. In November, 1924, while at his clerical work, he suddenly dropped his pen and experienced a sensation of numbness over the right hand. This extended down to the elbow, and three weeks later he observed burning pains in the right shoulder and right side of the chest posteriorly. A diagnosis of syphilis was made, and he received antisyphilitic treatment. About March, 1925, he noticed a bulging of the left eye. At this time he received roentgen treatments to the chest. The shooting pains extended to the left leg, and a few weeks later difficult and painful urination developed.

Physical Examination.—The patient was poorly nourished and markedly emaciated. He was confined to bed, with the lower extremities flexed on the abdomen. The left eyeball was more prominent than the right. The left side of the chest was bulging. The expiratory movements on the right side were limited from the apex to the base. There was absent vocal fremitus over the entire right side, with dulness to flatness from the third rib down. There were diminished to almost absent breath sounds on the right side from the third rib to the base of the lung. The blood pressure was 110 systolic and 74 diastolic.

Neurologic Examination.—The left pupil was greater than the right; both were irregular and both reacted sluggishly to all stimuli. There was nystagmus in the right-left lateral gaze. All the deep reflexes were increased. The knees were flexed on the abdomen. There was marked tenderness of the left hip. There was a definite zone of hyperesthesia, hyperalgesia and hyperthermesthesia on the right side, corresponding to the fourth and fifth dorsal vertebrae.

Laboratory Data.—Roentgen examination showed a dense homogeneous shadow from the apex to the diaphragm on the right side. The dorsal spine disclosed a partial collapse of the tenth dorsal vertebra. Examination of the hips showed a marked destruction of the acetabulum, especially at the upper half, with bone production. Examination of the sputum revealed tumor cells. The surgical specimen following paracentesis consisted of a few fragments of tissue made up of regular columns of foamy cells and small round nuclei.

Diagnosis.—The diagnosis was carcinoma of the lung with metastases to the spine.

Comment.—The tumor cells found in the sputum and pleural fluid, the roentgen observations on the chest and the partial collapse of the tenth verebra with a definite picture of a transverse lesion of the spinal cord, pointed toward metastasis to the vertebral column. Nystagmus, as already observed by Elsberg and others, is not an uncommon observation in cases of lesion of the spinal cord, most likely due to involvement of the posterior longitudinal bundle.

Case 3.—*History.*—S. C., a man, aged 47, a merchant, was admitted to the hospital on Sept. 4, 1926. In July, 1925, he had a dull pain over the right shoulder joint, which incapacitated him for work. A diagnosis of tuberculosis was made, and he was sent to Saranac Lake. In July, 1926, his speech became impaired; he stammered and at the same time dizzy spells and headaches developed. A diagnosis of carcinoma of the lung was made following a biopsy in September, 1926.

Physical Examination.—Examination revealed an unstable patient with a masklike expression of the face. The left half of the chest was slightly larger than the right. There was an impaired percussion note bordering to flatness over the left side of the chest from the fifth rib down. The breath sounds were diminished over these areas. The heart was normal.

Neurologic Examination.—The pupils were normal and reacted to all stimuli. The right forearm, arm and hand showed atrophy of the muscles. The power of the right hand was poorer than that of the left, and the entire shoulder joint and back were one solid mass. Movements of the shoulder joint were limited. There was some hyperesthesia over the right upper extremity. The patient was disoriented for time, was apathetic, restless and emotionally unstable and had definite memory defects. There were no illusions, delusions or hallucinations. He was discharged from the hospital on Oct. 3, 1926.

Laboratory Data.—A roentgenogram of the chest showed a pleural effusion on the left side extending from the diaphragm up to the fourth rib in the axillary line. Above this there was a complete pneumothorax, the upper lobe being collapsed down to a small mass. The heart and mediastinum were pushed to the right. There was a dense mass around the right shoulder joint, with a destructive process involving the entire scapula and the outer and middle thirds of the clavicle suggesting a neoplasm. Examination of the skull failed to reveal any metastases. Other laboratory examinations gave negative results. Fluid tapped on Sept. 20, 1926, was hemorrhagic and contained tumor cells suggesting a primary neoplasm of the lungs.

Diagnosis.—The diagnosis was carcinoma of the lung, with secondary involvement of the right shoulder, brain and liver.

Comment.—The character of the tumor cells from the fluid, the biopsy in 1926, and the mental and neurologic signs pointed toward involvement of the central nervous system, as well as the right brachial plexus. As in many other cases, during the early course of the disease, a diagnosis of pulmonary tuberculosis was considered. This patient died at home, and an autopsy was not secured.

CASE 4.—A. K., a woman, aged 56, a housewife, was admitted to the hospital on Oct. 1, 1927, complaining of cough, loss of voice and gradually increasing weakness of the left half of the body. The onset took place one year before admission to the hospital, with chills and fever; the condition was diagnosed bronchitis. In February, 1927, the patient began to complain of flushing of the face, dry tongue and paresthesias of the face and arms, with a gradual paralysis of the left side of the body. She was taken to a hospital, where a diagnosis of chronic encephalitis was considered. There paroxysmal attacks of coughing developed, and toward the end she became hoarse and aphonic. She had two convulsions, preceded by attacks of aphonia without loss of consciousness.

Physical Examination.—Examination showed a well nourished, somewhat distressed woman with slight cyanosis of the lips and paralysis of the left side of the mouth. On percussion, flatness was found over the middle and lower portions of the left side of the chest and over the right angle of the scapula. Moist coarse râles were audible posteriorly over the entire right side of the chest. The breath sounds over the left side were diminished. The heart was normal.

Neurologic Examination.—Exophthalmos was noted. The fundi revealed changes incidental to a high myopia. Speech was reduced to a whisper. There was a definite left hemiplegia with active biceps and ankle jerks on both sides. There was a Babinski sign on the right. On Oct. 4, 1927, the patient had a jacksonian attack. She died on Oct. 25, 1927.

Laboratory Data.—A roentgenogram of the chest showed a pleural effusion on the right side extending to the sixth rib in the axillary line, possibly due to neoplasm. The blood count showed: hemoglobin, 50 per cent; red blood cells, 2,200,000; white blood cells, 14,800. The differential count was normal. A Wassermann test of the blood and spinal fluid was negative.

Diagnosis.—The condition was diagnosed neoplasm of the lung, with cerebral metastasis. The anatomic diagnosis was squamous cell carcinoma of the right lung, right bronchus, with extension and metastases to the bronchial lymph nodes and compression of the esophagus; chronic pyelitis and cystitis.

The brain and cord were not removed.

Comment.—Early during the disease, a diagnosis of chronic encephalitis was considered. Unlike most cases, the onset of the disease was gradual. The presence of the tumor in the lungs most likely was the explanation of the neurologic observations. The histogenesis of the tumor showed it to belong to the squamous cell variety.

CASE 5.—*History.*—S. S., a man, aged 53, a cap maker, was admitted to the hospital on Jan. 12, 1928, with paralysis of the lower extremities and loss of sensation below the nipple line, pain in the right side of the chest and bloody expectoration. The onset came on suddenly five months before admission with sharp pain in the right side of the chest, which was worse on coughing, followed

by loss of weight and weakness. He received four deep roentgen treatments over the chest, following which the cough became more productive and bloody. On January 23, the lower extremities became completely paralyzed, with loss of sensation to the nipple line. The paralysis was preceded for a few hours by a gradual weakness, clonic movements of both lower extremities and loss of control of the bladder and rectum.

Physical Examination.—The patient was a well developed man. The glands of the neck were somewhat enlarged in the supraclavicular region. There was irregular expansion on both sides of the chest with dulness at the left base and impaired note throughout the entire right side. The breath sounds were distant, with many moist, coarse and fine râles over the right side of the chest. The heart was normal.

Neurologic Examination.—The pupils were irregular; the right was larger than the left, and both reacted to all stimuli. There was a flaccid paralysis of both lower extremities with absent reflexes. All forms of sensation were lost from the eighth dorsal vertebra down. The biceps and triceps were elicited and were equal on both sides. There was retention of urine with a relaxed rectal sphincter.

Diagnosis.—The clinical diagnosis was carcinoma of the lung with metastases to the dorsal spine.

Laboratory Data.—Slight secondary anemia was present. The urine was normal. The patient died on Feb. 5, 1928.

The anatomic diagnosis was carcinoma of the upper lobe of the right lung, with invasion of the ribs and vertebral column; metastases to the bronchial and retroperitoneal lymph nodes; subacute urethritis and pyelitis and hypostatic pneumonia in the lower lobes of both lungs. The brain and cord were not removed. The microscopic diagnosis was primary carcinoma of the lung originating from the bronchi.

Comment.—The sudden onset, the definite primary carcinoma of the lung and the level lesion of transverse myelitis at the eighth dorsal vertebra pointed to metastases to the vertebra. The cerebral symptoms were completely absent.

The analysis of the cases that came to autopsy (sixty-one in all) showed fifty-seven of the tumors to be bronchial in origin; two were squamous cell carcinomas, one originated from the alveoli of the lungs and one belonged to the primary endothelial type of tumor. The histopathology of these types of tumors is fully covered by Ewing,[7] Moise[8] and others, and for a detailed account the reader is referred to these authors.

In group 1 the ages ranged from 34 to 70; the average duration of the tumor was about from one to one and one-half years, with the exception of case 2 in which the patient lived nine years and case 3 in which the patient lived six years. The pulmonary signs came on sud-

7. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922, pp. 809-815.

8. Moise, T. S.: Primary Carcinoma of the Lungs, Arch. Int. Med. **28**:733 (Nov.) 1921.

denly in four cases, the cerebral signs came on suddenly in all six cases, and the symptoms in the spinal cord came on suddenly in one case. A diagnosis of primary carcinoma of the lung was considered in four of the cases, with the exception of cases 4, 5 and 7. In case 4 a diagnosis of dementia paralytica and bronchopneumonia was made, although a primary neoplasm of the cerebrum was considered as a remote possibility. The predominance of the paretic picture diverted the clinician's attention from the observations on the chest. Histopathologic observations confirmed the diagnosis of dementia paralytica and a metastatic carcinomatous nodule to the cerebellum.

In cases 5 and 7 a diagnosis of chronic fibroid phthisis was made. The neurologic symptoms, with the exception of headache and tinnitus, were negative, and for this reason involvement of the nervous system was not considered. The diagnosis of pulmonary tuberculosis is frequently made instead of primary pulmonary carcinoma of the lung. Occasionally cases are found in which the patients have both tuberculosis and carcinoma of the lung. Cases 3 and 5 fall in this group. Tuberculosis has been considered as a cause of primary carcinoma of the lungs by Ewing [7] and other investigators. Statistics on the incidence of this occurrence vary to such an extent that one has to be guarded in drawing definite conclusions.

Of the seven cases showing metastases to the central nervous system, three had a single metastasis and three multiple metastases, and one showed a single metastasis causing compression of the spinal cord. Metastases to the cord itself are rare. Simpson [1] found only one case in a series of thirty cases, twenty-nine of which showed involvement of the vertebral column. The occurrence of more than a single metastasis is frequently observed at autopsy. When a single nodule is found, a careful search will reveal other minute nodules (fig. 10). When single metastases occurred, as in cases 3 and 4, these showed involvement of the cervical lymph glands. This induced us to agree with Hassin's view that tumor cells may be carried from the lymph glands of the neck by a backward flow of the lymph along the perineural spaces of some cranial nerves to the subdural or subarachnoid spaces and ultimately to the brain substance. When tumor cells are carried by the blood stream, the likelihood is that the central nervous system will show multiple and not single metastases.

The histogenesis of the tumor in these cases showed them to be bronchial in origin.

In group 2 the ages varied between 47 and 57. The duration of illness was about the same as in group 1. The onset of pulmonary and neurologic symptoms was sudden in cases 1, 2, 3 and 5 and gradual in case 4. The condition in all these cases was diagnosed primary carcinoma of the lung. Two of the cases showed a transverse lesion

of the spinal cord, symptoms of which were undoubtedly due to secondary deposits in the vertebral column causing compression of the cord. Case 2 disclosed a partial collapse of the tenth dorsal vertebra, which was verified at autopsy. Only two of the cases in this group in which the condition was diagnosed as carcinoma of the lung came to autopsy (cases 4 and 5), and the brains and spinal cords were not removed.

SUMMARY

A group of 12 cases selected from 109 in which the condition was diagnosed as primary carcinoma of the lung were studied from the point of view of metastases of the central nervous system.

Three cases showed symptoms of the spinal cord due to compression following invasion and destruction of the vertebra by the metastases. Of 109 cases of primary carcinoma of the lungs investigated, 11 per cent showed involvement of the central nervous system. One of the cases came to autopsy and revealed compression and distortion of the cord without circulatory interference. The spinal cord is rarely the seat of metastasis from primary carcinoma of the lung.

The onset in most of the cases showing neurologic signs came on suddenly. The neurologic signs may be present without any evidence of pulmonary changes. For both diagnostic and therapeutic reasons, thorough examination and roentgenograms of the chest are advisable in every case in which tumor of the brain is suspected.

Metastases to the central nervous system may be single or multiple. When multiple metastases are found, the theory of tumor cells being carried by the blood stream to the brain is favored. When a single metastasis is found, a direct extension by a backward flow of the lymph to the brain due to involvement of the cervical lymph nodes is favored.

The most frequent histologic types of primary carcinoma of the lung with or without metastases to the central nervous system were those derived from the bronchi.

PERIPHERAL ARTERIAL DISEASE IN POLYCYTHEMIA VERA *

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The commonest complications of polycythemia vera are those of the vascular tree. The frequency of thrombosis is generally recognized, and it is demonstrable that venous thrombosis is present in the majority of cases of polycythemia vera when they are first seen. The high incidence of thrombosis seems to be adequately explained by the huge increase in the volume of circulating blood of high viscosity. After the disease has persisted for a time, sluggish circulation, with chronic passive congestion, becomes exaggerated. The rate of circulation, as tested by the histamine method, when measured from leg to face or arm to face, is from five to ten times slower than that in the normal subject. There are changes in the blood, also, which favor thrombosis; high viscosity, hypercalcemia, and an increase in the number of platelets doubtless are important.

The arterial diseases associated with polycythemia vera have not been extensively studied. An impression has been gained from roentgenograms of the peripheral arteries, in cases of polycythemia vera, that abnormal grades of calcification exist, especially in patients of advanced age. The symptoms and the appearance of the retinal vessels have led to the suspicion that cerebral arteriosclerosis is common. Peacock, in a recent study, has shown that the arterial pressure is not increased to a significant degree in polycythemia vera, in spite of the huge increase in the volume of blood. The lack of accurate data on the subject led to this study of a group of cases of polycythemia vera in which certain features seemed to be secondary to arterial disease.

MATERIAL USED FOR THE PRESENT STUDY

One hundred cases in which the diagnosis of polycythemia vera had been made were reviewed with reference to symptoms which might be regarded as indicative of peripheral arterial disease. This series includes all of the cases seen at the Mayo Clinic from May 1, 1912, to Jan. 1,

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* From the Division of Medicine, the Mayo Clinic.

1929. In the latter years, the diagnosis was measurably fortified by studies of blood volume. No cases have been included in which the likelihood of polycythemia vera being present had been graded, at the time of diagnosis, as less than 75 per cent. The features of each case have been reviewed in detail and the diagnoses verified. All cases in which obvious thrombosis of peripheral veins was present have been excluded. Of this number, twenty-seven cases (27 per cent), presented a major complaint referable to the extremities, which suggested disease of the arteries of the extremities. In view of lack of special interest in the problem, and incomplete studies in most of the early cases, it is almost certain that the figures given represent an underestimate of the incidence of the conditions considered. The observations reported, however, are the result of a more intensive interest developed in recent years, and are in themselves, to our minds, satisfactory. These cases were classified in three groups: a group of arteriosclerotic patients, a

TABLE 1.—*Polycythemia Vera*

Total cases		100
Cases in which major complaint is referable to extremities (not including those of venous thrombosis)		27
1. Arteriosclerotic disease		20
a. Claudication without demonstrable occlusion	6	
b. Arterial occlusion with gross gangrene	1	
c. Acroparesthesia (burning type)	13	
2. Thrombo-angiitis obliterans		1
3. Vasomotor disturbances		6
a. Dilator type (some features of erythromelalgia)	3	
b. Spastic type (features suggesting Raynaud's disease)	3	

group with thrombo-angiitis obliterans, and a group in which vasomotor disturbances were prominent (table 1).

ARTERIOSCLEROTIC DISEASE

In these cases sclerosis and calcification of the arteries of the extremities were present in a greater degree than was felt compatible with the age of the patient. The symptoms were attributable to arterial insufficiency.

Claudication.—In the six cases of arteriosclerosis of the extremities in which there was claudication, without occlusion of palpable arteries, claudication was a definite and disabling symptom. Distress on exercise was usually localized in the feet and calves of the legs; in two cases, claudication was bilateral. Exercise was restricted after periods of walking from two to six city blocks. Relief was obtained by standing still for short intervals, after which exercise could be resumed. In all the cases of this group, high grades of calcification were represented in the roentgenograms.

The effects of treatment in this group of six cases were striking. In every instance, following the administration of phenylhydrazine, and reduction in the total volume of blood, tolerance to exercise increased markedly. In three cases, the clinical symptoms disappeared entirely, and in the remaining three they were markedly improved. Calorimetric studies were carried out in two cases (fig. 1). In these, the rate of elimination of heat was determined by the Stewart-Kegerreis calorimeter. It was found in one case in which the blood volume was 136 cc. for each kilogram of body weight that 0.55 calory was eliminated for each square inch of surface area for each minute of time. Follow-

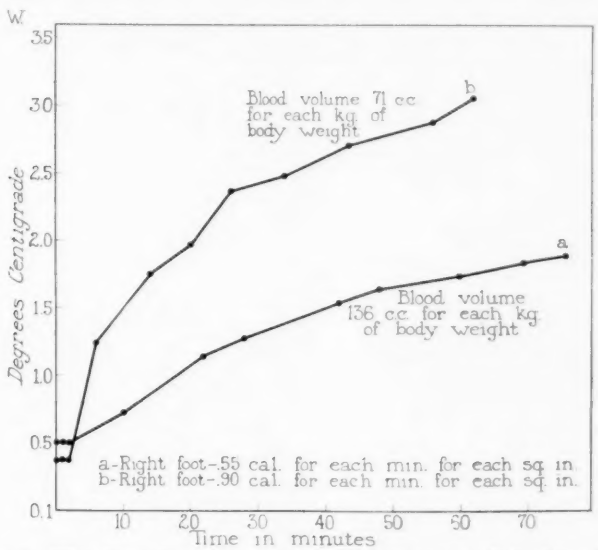

Fig. 1.—The effect of reduction of blood volume on the elimination of heat in arteriosclerosis of the extremities with claudication associated with polycythemia vera.

ing treatment, the blood volume became reduced to 71 cc. for each kilogram of body weight, and the amount of heat eliminated increased to 0.9 calory, with alleviation of the symptoms. The patient was observed for various periods, and it was found that when the blood volume and the concentration of erythrocytes and hemoglobin increased to approximately the levels that had been maintained before treatment, claudication reappeared. A similar study was carried out in a case in which the symptoms were the same as in the one just mentioned. Following treatment, and reduction of the volume of blood, only a slight increase in the rate of elimination of heat was demonstrable, and the symptoms of claudication were not entirely relieved.

Arterial Occlusion with Gangrene.—It might be expected that gangrene of arteriosclerotic origin would be relatively common in this disease; however, only one case of this type was encountered. In order to obtain more accurate information on this point, studies of blood volume have been made in cases of gangrene of arteriosclerotic origin. In several cases of gangrene, there was relative polycythemia, in which the number of erythrocytes for each cubic millimeter of blood and the concentration of hemoglobin, was increased, but the blood volume was not above normal limits. These cases of relative polycythemia were similar to the type described by Geisböck as polycythemia hypertonica. The patient with true polycythemia and arteriosclerotic gangrene was a senile man, aged 78. When he was first seen he had bilateral pedal gangrene, with an excessive degree of generalized cyanosis. Because of excessive pain he had taken many tablets presumably containing derivatives of coal tar. Spectroscopic examination of the blood disclosed the presence of sulphemoglobin. He had 171 cc. of blood for each kilogram of body weight. The spleen was moderately enlarged, and the number of erythrocytes and the percentage of hemoglobin were high. His condition was so critical that operative measures could not be carried out. He returned home, and died within a month.

Acroparesthesia.—Thirteen patients in this series gave as their major complaint a burning sensation of the feet. Cases were not included in which numbness and creeping paresthesia were prominent. The usual symptoms were burning distress with exercise, or at night alternation of coldness of the limbs with burning distress, and cramps of the muscles of the calf. Accurate segregation of the patients with acroparesthesia, and those with a vasodilator syndrome, was accomplished by thermometric and calorimetric studies during the stages of burning. Three groups could be distinguished: (1) patients with acroparesthesia, without variations in the surface temperature in the stages when there was burning; (2) patients with acroparesthesia and slight increases in surface temperature during the symptomatic period, insufficient, however, to be considered significant as a causative factor in the complaint, and (3) patients with a true vasodilator syndrome, with high surface temperature and other phenomena making possible the diagnosis of erythromelalgia. The third group is considered under the dilator type of vasomotor disturbance; the first and second groups are classified as true acroparesthesia. Neurologic changes were not demonstrable in this group with acroparesthesia. Calcification and coldness of the feet were common; claudication was absent. The explanation of the frequency of this syndrome in polycythemia vera is not clear, although many theories have been advanced.

Müller suggested a vasoneurotic basis, which is not borne out by our studies. Cassirer suggested disturbance of the sensory nerve endings, to which opinion we incline. Our conception of the disturbance postulates atrophy of the outer layer of the skin secondary to vascular changes in the smaller arteries of the skin, probably on an arteriosclerotic basis. Irritation of nerve endings results from stimuli not ordinarily perceived in normal skin. Vasomotor reflexes of a vasoconstrictor type would also be present in many instances.

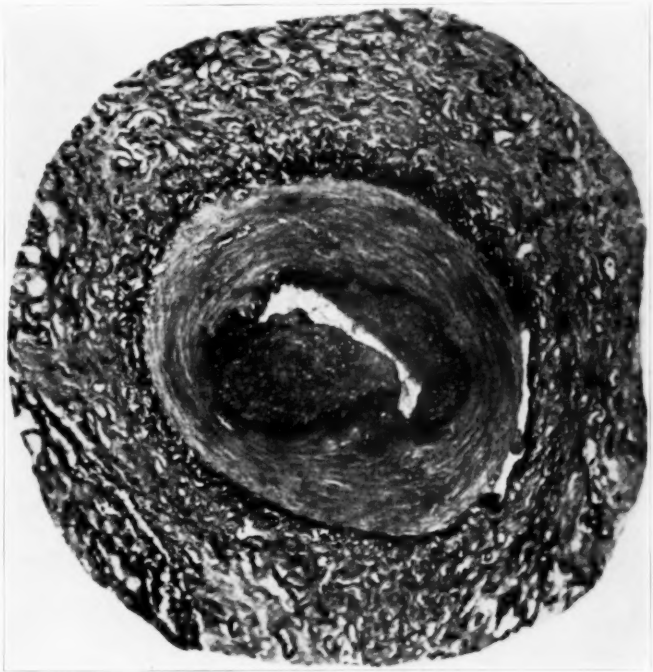

Fig. 2.—Appearance of artery in polycythemia vera and thrombo-angiitis obliterans. The partial occlusion of the arterial lumen is due to intimal proliferation. A thrombus is not shown in this area. Weigert's stain is used to show proliferation of the elastic tissue.

In this group of cases there is absence of relief following reduction of blood volume. Indeed, no form of treatment has been successful in relieving this burning paresthesia. Contrast baths and cinchophen have given only slight symptomatic relief. Apparently, increased viscosity and a slow rate of circulation are not direct factors in the production of acroparesthesia.

THROMBO-ANGIITIS OBLITERANS

One patient with a proved case of thrombo-angiitis was observed. The patient, an American born gentile, aged 52, came to the clinic with gangrene of the first toe on the right foot. Because of his heightened facial color, the volume of the blood was determined, and was found to be 160 cc. for each kilogram of body weight. Improvement was not effected in the condition of the extremity by reduction of blood volume and the right leg was amputated. Figure 2 shows the appearance of the arteries. The pathologic picture was that of a mixed lesion. There was definite arteriosclerosis, as was shown by the calcification of the

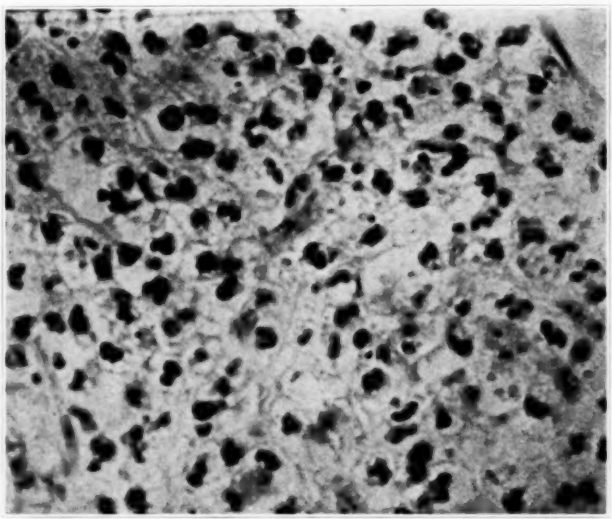

Fig. 3.—Appearance of cells in occluding thrombus. Lymphocytes and polymorphonuclear cells predominate.

media, but the occluding thrombus was of the inflammatory type (fig. 3). Magnification under high power disclosed the presence of many polymorphonuclear leukocytes and lymphocytes. In the outer coats of the arteries, also, there was definite inflammatory reaction. Weigert's stain (fig. 2) revealed great thickening of the intima in the nonthrombosed areas. There was marked proliferation of the elastic tissue layer.

VASOMOTOR DISTURBANCES

Dilator Type.—Three patients of the series presented symptoms suggesting erythromelalgia. There were excruciating degrees of burning, usually in certain areas on the plantar surfaces of the feet. The

burning was intermittent and was aggravated by heat and exercise, and by a dependent position of the extremity. Moderate relief was obtained by elevation of the feet and by applications of cold. During the attacks, the feet or hands would become excessively red, the veins engorged, and the surface temperature of the painful area markedly elevated. The data in one of these cases are shown in table 2. The patient was a Jew who presented a picture of vasodilator neurosis involving his left foot. The fact that the disorder was unilateral separated it from the syndrome described by Mitchell which is always bilateral. When

TABLE 2.—*Thermometric Studies of a Case of Unilateral Erythromelalgia and Polycythemia Vera in a Man, Aged 25*

	Temperature, C.					
			Skin			
Date	Mouth	Room	Right Great Toe	Left Great Toe	Position	Comment
1/ 2/28	37	22	27.5	34.3	Patient at rest	Blood volume 203 cc. for each kilogram of body weight
			31.0	34.8	Patient at rest	Burning pain in left foot
			30.1	33.2	Feet up 45°	
			30.0	34.1	Feet up 90°	
			30.3	34.1	Feet down 45°	
			28.8	33.8	Feet down 90°	
			28.3	33.8	Blood pressure cuffs above the knees cutting off pulse of both feet	
			27.5	33.5	Patient at rest	
			29.0	34.3	Feet up 90°	
			30.7	34.1	Rapid walking exercise	
1/19/28	37	22	29.7	31.9	Patient at rest	No distress in left foot
			29.3	31.9	Patient at rest	
			27.5	28.7	Feet up 45°	
			31.1	31.9	Feet up 90°	
			29.7	31.5	Feet down 90°	
			28.2	30.0	Rapid walking exercise	
1/21/29	..	..	....	....	.....	Blood volume 150 cc. for each kilogram of body weight. Relief 70 per cent in left foot

the patient was first examined, he had 203 cc. of blood for each kilogram of body weight. The surface temperature of the affected foot, during the attack, increased to 34.3 C. (93.5 F.), while that of the opposite foot was 27.5 C. (81.5 F.) (fig. 4). Calorimetric studies disclosed definite differences in the rate of elimination of heat as measured in small calories in the two feet (fig. 5). It was found that elevation of the foot diminished the temperature on the affected side appreciably, whereas on the normal foot only a slight change occurred. Likewise, cutting off the circulation on both sides for a period of fifteen minutes produced no lowering of the cutaneous temperature on the affected side, but a slight reduction of that of the skin of the normal foot. With the reduction of the blood volume to 150 cc. for each kilogram of body

weight, relief of approximately 50 per cent was produced in the symptoms. Reports from this patient obtained during the ensuing year have indicated persistence of vasomotor disturbances; the intensity of the symptoms increases and decreases with some apparent relationship to the polycythemia, but at no time has complete relief been obtained. Figures 4 and 6 show the surface temperatures of the right foot and the left foot, and the effects of posture, exercise and weight-bearing on the surface temperatures. The marked difference between the feet is striking.

The second case of the series was that of a woman, aged 72, who was first seen in 1926 complaining of paroxysmal attacks of burning

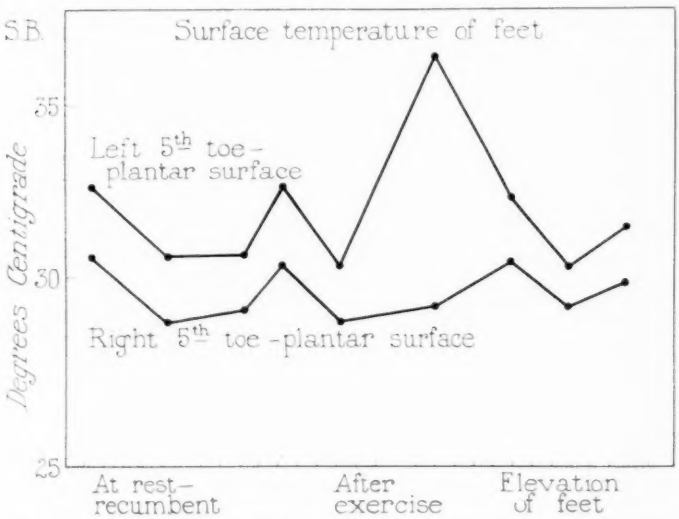

Fig. 4.—Increase in the surface temperature in a case of unilateral vasodilator disturbance, at rest, after exercise and with elevation of the feet.

feet, which were induced by exercise, and by covering the feet in bed. The symptoms suggested the syndrome seen in older subjects with arteriosclerosis. The elevated surface temperature during attacks, however, demonstrated that this was a true vasodilator disturbance. At this time, 1926, the concentration of hemoglobin and erythrocytes was normal, whereas the viscosity of the blood was somewhat high, 6.3. The patient was carefully observed at home for the next two years, at the end of which time she returned for detailed examination. It was then found that the vasomotor disturbances had entirely disappeared, and that definite evidence of polycythemia vera had developed. The volume of blood was 191 cc. for each kilogram of body weight, and mild hyper-

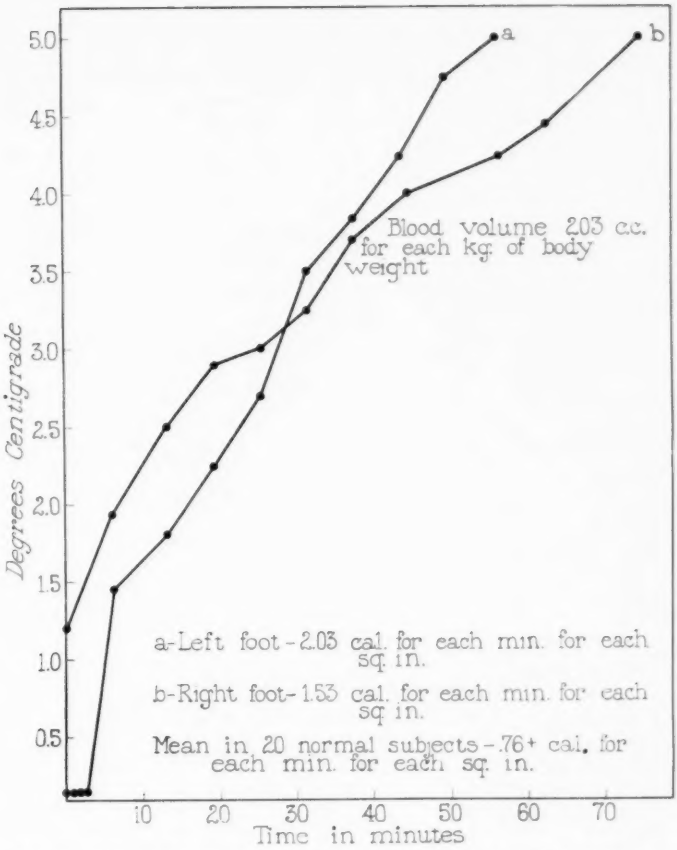

Fig. 5.—Rate of the elimination of heat as measured in small calories for each minute for each square inch of surface area. Sharp differences are shown in the right and left foot. The mean for normal subjects is given.

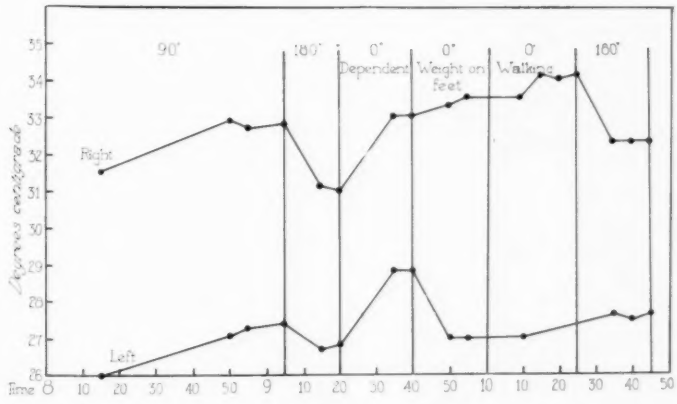

Fig. 6.—Effects of posture, weight bearing and walking on the surface temperature of the feet.

tension was present (table 3). The temperature of the surface of the extremities at this time was normal, varying between 26 and 28 C. (78.8 and 82.4 F.), and peripheral symptoms were absent.

The third case was similar to the second case. The patient was aged, and complained of burning extremities in which the surface temperatures and calorimetric studies indicated vasodilator disturbances. The blood volume was 150 cc. for each kilogram of body weight. The clinical appearance was that of polycythemia vera; splenomegaly was present. Marked improvement was obtained in this case by reduction of the blood volume.

TABLE 3.—*Data in a Case of Erythromelalgia in a Woman, Aged 72*

	Temperature, C.					
			Skin Temperature of Foot			
Date	Mouth	Room	Right Dorsum	Left Plantar Surface	Left Dorsum	Comment
1/15/26	....	22	34.4	....	35.5	Paroxysmal attacks of hot burning feet induced by exercise and bed covers
9/22/26	37.1	23	....	34.7 35.0	34.7 35.2	
9/24/26	36.1	22.4	....	36.0 35.3	35.0 34.6	Blood data: hemoglobin, 16.5 Gm. for each 100 cc., 4,920,000 erythrocytes for each cubic millimeter; viscosity, 6.3
9/29/26	....	..	....	35.1 35.5	34.4 34.7	
9/ 4/28	....	..	....	....	....	Patient returned with complete relief from symptoms in feet; diagnosis: polycythemia vera (191 cc. of blood for each kilogram of body weight) and hyperthyroidism

Spastic Type.—Vasomotor disturbance of the spastic type was relatively rare. This seems rather surprising in view of the fact that vasospasm of the smaller arterioles involving single digits is not uncommon in cases of arteriosclerosis. In three cases, attacks of pallor occurred, which involved single digits, and were asymmetrical in distribution. This is the so-called "dead finger" syndrome, or the single phase color reaction observed in the secondary forms of vasomotor disturbances of the spastic type. Recovery of the arteriolar spasm was easily induced by immersion of the hands in warm water or by active massage. Trophic changes were not observed. Microscopic examination of the surface capillaries revealed the long, narrow, contracted loops seen in cases of arteriosclerosis. The dilated atonic capillary loops of Raynaud's disease were absent. Reduction of blood volume in these cases caused complete disappearance of the symptoms.

COMMENT

The clinical analysis of this group of cases indicates that disease of the peripheral arteries is relatively common in polycythemia vera and that it may cause unusual symptoms and aberrant manifestations. The recognition of this fact makes one responsible for excluding polycythemia vera in all cases which present evidence of peripheral vascular disease. The cases with claudication, without demonstrable closure of the large arteries of the extremities, are of particular significance. Two factors probably are operative: 1. There is an organic factor resulting in narrowing of the lumen of the smaller arteries. 2. Anoxemia is caused by marked reduction in the rate of circulation. Direct observation of the flow of blood through the surface capillaries in cases of polycythemia vera demonstrates extreme sluggishness of flow. The capillary blood is close to the threshold of cyanosis, and moderate decreases in environmental temperature cause complete stasis of the blood in the loops, and produce cyanosis of the capillary blood. Recent studies have demonstrated similar retardation in the flow of blood in the larger vessels. The utilization of oxygen in the extremities of patients with polycythemia vera, as determined by the oxygen content of arterial and venous blood, is increased. Claudication, which is an expression of anoxemia, may be largely of a functional type. The supply of oxygen to muscle may be impaired by the increased viscosity of the blood and retardation of its flow, and perhaps organic changes in the walls of the capillaries prevent adequate exchange of oxygen. A correct diagnosis of the underlying condition is important because so frequently reduction in blood volume and viscosity results in symptomatic improvement and return to almost normal activity.

Only one case of occlusion of the arteries, with gross gangrene, was observed, and this occurred in an aged patient. This incidence is in marked contrast to the occurrence of venous occlusion.

The association of thrombo-angiitis obliterans with polycythemia vera is rare; the case reported here is the second in the literature. Weber described a similar case in a Jew, aged 43, the clinical description of which is satisfactory although pathologic proof was not obtained. One of us (Brown) has had the opportunity of observing a large number of cases of thrombo-angiitis obliterans in which studies have been made on the viscosity of the blood, the blood volume, and the concentration of erythrocytes and hemoglobin, and in no other case has polycythemia vera been encountered. This is of especial interest because it has been frequently suspected that changes in the blood are a factor in thrombo-angiitis obliterans, chiefly in the production of thrombosis; this hypothesis has led to the use of anticoagulants. There is no evidence, however, to indicate that this is true.

The cases of paresthesia associated with polycythemia vera are similar to those observed in older arteriosclerotic patients without polycythemia. The usual complaint is of a burning sensation in the feet, but not confined to the areas of pressure. Such cases should be distinguished from those in which there are predominant vasodilator disturbances. This can be done by means of measurements of the surface temperatures of the painful areas before and after exercise, and with different postures. In pseudo-erythromelalgia the temperature of the surface of the affected part is normal or low, although the patient states that the affected areas burn. Reduction of blood volume has less effect on the symptoms in the cases of simple paresthesia than in those with demonstrable vasodilator disturbances.

Cases of polycythemia vera, with painful vasodilator disturbances, are not unusual. Weber has described cases of this type. It is suspected, however, that Weber has confused the erythromelalgia of Mitchell with the rubor seen in cases of thrombo-angiitis obliterans and arteriosclerosis with occlusion of the arteries. It is not the color of the extremities that determines the diagnosis of erythromelalgia, but an increased volume and flow of blood through the extremities, accompanied by redness and distressing symptoms, and proved by an increased surface temperature during the attack. Erythromelalgia is an extremely rare condition. The diagnosis rests on the criteria first described by Mitchell; intermittent periods of vasodilatation of the extremities are associated with redness, burning hyperhidrosis and dilated, throbbing veins. In the cases described by Mitchell, the disturbances were symmetric and bilateral. Cases with unilateral disturbance have not been observed in our experience, except in association with polycythemia vera, and even in these cases vasodilatation was present in both feet, but was more marked and produced symptoms in one foot. All cases of erythromelalgia which have come under observation in recent years have been studied from the standpoint of the possible existence of polycythemia vera; in this way two cases have been detected. Spastic phenomena of the Raynaud type were present in three cases, and the reduction of blood volume effected complete relief.

Our endeavor to estimate the incidence of symptoms due to peripheral arterial disease in polycythemia vera is based largely on records; only recent cases have been studied in detail. The classification can be regarded as satisfactory, but the percentage of occurrence may later need to be revised.

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ACUTE MONOCYTIC (HISTIOCYTIC) LEUKEMIA

REVIEW OF THE LITERATURE AND CASE REPORTS *

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The conception is still general that but two types of leukemia exist: myelogenous, arising from the bone-marrow, and lymphatic, arising from the lymphoid tissue. That there is a third form of leukemia, arising from the reticulo-endothelial (histiocytic) system and characterized hematologically by an extreme degree of monocytosis and histiocytosis, is not as yet well recognized. Comparison of the reported cases indicates their similarity and emphasizes the existence of a clearcut entity, monocytic leukemia. Reschad and Schilling-Torgau,[1] in 1913, were the first to describe this "new" form of leukemia. Since then twenty-six cases have been reported. The most complete studies have been made by Merklen and Wolf.[2] The present communication describes the observations in two additional cases.

REPORT OF CASES [3]

CASE 1.—*History.*—M. R., a Jewish business man, aged 55, was admitted to the hospital on Oct. 21, 1928, complaining of swollen gums. The family and marital history were not significant. He had felt well until 1926, when several teeth were extracted because of abscess formation. In October, 1927, the right submaxillary gland was removed because of calculi in the duct. At that time he had felt slightly depressed and had noted occasional pain in the flanks, relieved by rest. During the summer of 1928, he suffered from pain at the left costal margin, particularly on taking a deep breath. One month before entry to the hospital, his gums became painful and swollen. He had consulted several dentists, and the diagnoses of Vincent's angina, pyorrhea and abscess formation were considered. Four lower teeth were extracted. The gums did not heal, and pain became severe. When the patient was finally admitted to the hospital he was unable to sleep and was markedly depressed.

Examination.—Physical examination showed a short, rather stocky man who was quite apprehensive. The buccal mucous membranes were slightly reddened

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1. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wchnschr. **60**:198 (Sept. 9) 1913.

2. Merklen, M., and Wolf, M.: Monocytes, monocytoses, leucémies à monocytes; trialisme leukocytaire, Presse méd. **35**:145 (Feb. 2) 1927; Leucémies à monocytes, Rev. de méd. **45**:154, 1928.

3. I am enabled to report the first case through the kindness of Dr. Harry Linenthal of the Beth Israel Hospital.

and swollen. The gums of the lower teeth were much inflamed, edematous, tender and spongy. The gums of the upper teeth showed similar, though not so marked, changes. Many of the lower teeth were missing. The tonsils, of moderate size, were apparently not diseased. A scar was present over the right submaxillary region. The heart and lungs were normal. The liver was definitely enlarged, its upper border being at the fifth rib and its lower border being felt threefinger breadths below the right costal margin. The spleen was not palpable. The skin showed slight pallor; there was no icterus or petechial spots. There was no apparent enlargement of the lymph nodes. The reflexes were normal. The temperature was 100 F., and the pulse rate, 100 per minute.

Laboratory Data.—Blood studies done as a routine gave striking observations: hemoglobin (Tallqvist), 70 per cent; red blood cell count, 4,500,000 per cubic millimeter; white blood cell count, 31,200. The differential count of the white blood cells showed: polymorphonuclear cells, 21.5 per cent (19 per cent mature, 2 per cent metamyelocytes, 0.5 per cent myelocytes); eosinophils, 0.5 per cent; lymphocytes, 12.5 per cent; monocytes, 65.5 per cent.

The monocytes were of two distinct types. The first type was the ordinary large mononuclear cell of the blood stream, from 12 to 18 microns in diameter, with grayish-blue cytoplasm containing innumerable, very fine azure granules; the nucleus was usually bean-shaped and was composed of a fine reticulum without nucleoli. The second type of monocyte was apparently the "type cell" of this blood picture. This was a very large, round or polygonal cell from 20 to 50 microns in diameter. Its cytoplasm was weakly basophilic. The cell boundaries were indistinct and irregular and pseudopods, or budding of the cytoplasm, were common. There were many granules, rather coarser and redder than in the ordinary monocyte and almost always grouped about the nucleus, hardly ever in the periphery of the cell or in the pseudopods. This peculiar distribution gave the cell a distinctive appearance. The nucleus was violet (Wright's stain), round or oval and "spongy." In color, form, size, distribution of granules, shape, size and character of nucleus, the cell was typical of the hemohistioblast of Ferrata [4] and of the histiocyte of other authors. Cells intermediate between the typical histiocyte and the typical monocyte could be seen.

Oxidase staining of the blood smear by the method of Sato and Yoshimatsu [5] showed the ordinary monocytes to be oxidase-positive, the granules being very fine, more sparse and less blue than in the polymorphonuclear cells. The immature monocytes or histiocytes were oxidase-negative. Supravital staining of the blood was done by the method of Sabin [6] and showed the large cells to be extremely active. At 37.5 C. their ameboid motion was very striking. There was continual alteration in both the size and the shape of the cells. Long streamers or pseudopods were constantly being sent out; these were seen to be wholly without granules. If the pseudopod remained stationary for a short time, a few granules would appear in it. One cell was seen with a red blood cell inclusion; the frequent and marked changes in size and shape of this cell were striking. The ordinary monocyte was not so active, and there was typical clustering of neutral red granules in the bend of the nucleus. However, no clear dividing line could

4. Ferrata, A.: Le emopatie, Milano, Societa Editrice Libraria, 1918.

5. Sato, A., and Yoshimatsu, S.: The Peroxidase Reaction in Epidemic Encephalitis, Am. J. Dis. Child. **29**:301 (March) 1925.

6. Sabin, F. R.: Studies of Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

be drawn between the histiocytes and the monocytes. There was marked differentiation, however, between these cells and the polymorphonuclear cells and lymphocytes. These distinctions have been well described by Sabin and others.

The case rapidly resolved itself into one of acute leukemia. Because of the high white count, the marked monocytosis with the presence of many histiocytes, the fever and the hepatic and later splenic enlargement, the diagnosis of monocytic leukemia was made. Lymphatic leukemia could be ruled out because the lymphocytes were both relatively and absolutely decreased and because the type cell corresponded in no respect to the morphology of the lymphocyte. Myelogenous leukemia could also be ruled out because of the following considerations: relative and absolute diminution in the granular or myeloid cells, almost complete absence of myeloblasts, scarcity of myelocytes and rarity of eosinophils and basophils. There was only one other conclusion, that this was a case of monocytic leukemia.

The remainder of the clinical course of the case, with laboratory data, is given in table 1.

Case 2.—*History.*—J. D., a cobbler, about 70 years of age, was admitted to the Beth Israel Hospital, on May 17, 1930. There was nothing of consequence in the familial or past history. He was well until nine weeks before admission, when he tripped and fell down a flight of stairs, bruising his left leg. The leg became greatly swollen and painful, and there was pain in the lower part of the back. The pain gradually subsided, but four weeks before admission, a severe chill developed, followed by a temperature of 105 F. Fever had been present since that time. A week later, there was pain in the right flank, associated with frequency and urgency of urination. Two weeks before admission the right side of his throat became painful; at this time swollen glands were noted under the right jaw, and clinical signs of frontal sinusitis were present. The patient grew progressively weaker and paler, and lost 34 pounds (15.4 Kg.) during his nine weeks of illness. Examination on entrance disclosed an obviously sick man with marked pallor. Positive observations were: tenderness over the right frontal sinus, large tonsils and bean-sized lymph nodes at the angles of both jaws and in both supraclavicular fossae. No other lymph nodes could be felt, nor were the spleen and liver palpable. No petechiae were present.

Roentgenograms of the sinuses disclosed involvement of the right frontal, right ethmoid and right antrum; the spine showed callous formation at the anterior portion of the third thoracic vertebra, probably due to a fairly recent fracture. The Wassermann reaction and culture of the blood were negative.

The blood picture on admission was unusual; only 5.6 per cent of polymorphonuclear cells were present, there being a lymphocytosis and monocytosis with what were at first considered to be lymphoblasts. The latter, however, were soon found to be oxidase-positive, and were therefore called myeloblasts. As will be shown in table 2, there was at first an increase in the myeloblasts, followed, however, by a rapid recession; the monocyte percentage rapidly rose from 29.6 per cent on admission to 86.8 per cent on the day of death. Typical histiocytes in large numbers were seen on May 20; thereafter most of the cells appeared to be typical monocytes, though the cells were somewhat larger than the ordinary monocyte, the nucleus often being more round or oval, and without indentation. The ordinary monocyte took the oxidase stain faintly, a small number of fine granules being present; the histiocyte was always oxidase-negative, however. On May 21, 22 and 23, although by Wright's stain the percentage of mature or ordinary monocytes far exceeded that of the histiocytes, oxidase stain showed that the great majority

TABLE 1.—*Clinical Course and Laboratory Data in Case 1*

Date	Clinical Signs and Symptoms; Treatment	Temperature	Hemoglobin (Sahli), per Cent	Red Blood Cell Count	White Blood Cell Count	Polymorphonuclear Cells, per Cent	Mature, per Cent	Metamyelocytes, per Cent	Myelocytes, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Mature, per Cent	Histiocytes, per Cent	Eosinophils, per Cent	Basophils, per Cent
10/24/28	Blood cultures negative; pain lower left side of chest; sweating	98-101 F.	..	.....	72,600	....	....	...	...	....	....	....	....	...	...
10/26/28	Dr. George R. Minot felt spleen 6 cm. below costal margin; roentgen therapy to upper midchest	.....	..	.....	.....	....	....	...	...	....	....	....	....	...	...
10/27/28	Roentgen therapy begun over spleen	.....	60	3,105,000	36,800	23.0	21.0	2.0	...	21.0	56.0	34.0	22.0	...	...
10/29/28	.....	.....	..	.....	19,300	....	....	...	...	....	....	....	4.0	...	...
11/ 2/28	Pains in various joints; roentgen therapy over spleen	.....	52	3,040,000	30,800	14.0	13.5	0.5	...	25.5	60.0	6.5	53.5	...	0.5
11/ 5/28	.....	.....	54	2,830,000	32,400	....	....	...	...	....	....	....	....	...	...
11/ 9/28	Roentgen therapy over spleen...	.....	..	.....	54,200	51.0	....	...	...	27.0	20.5	19.5	1.0	1.0	0.5
11/12/28	Many Vincent's organisms found below the gums; neoarsphenamine given intravenously	.....	52	2,740,000 blood platelets 238,000 per c.mm.	48,800	35.5	....	...	...	21.5	41.5	8.5	33.0	...	...
11/16/28	Roentgen therapy over the gums with slight improvement	.....	..	.....	.....	....	....	...	...	....	....	....	....	...	...
11/19/28	Roentgen therapy over jaws (gums)	.....	50	2,560,000	37,600	39.5	....	...	2	17.5	41.5	9.5	32.0	...	...
11/21/28	.....	.....	..	.....	.....	23.0	21.5	2.0	...	7.5	68.0	8.0	60.0	...	...
11/23/28	Slight swelling and marked tenderness over anterior surface of right ankle joint; slight tenderness over lower ribs on left side; roentgen therapy over ribs and anterior spleen	.....	..	.....	.....	....	....	...	...	....	....	....	....	...	...
11/26/28	Vague pains; x-ray films of long bones negative	.....	.	.....	.....	....	....	...	...	....	....	....	....	...	...
11/27/28	Vital staining studies confirmed previous studies; sore throat; marked swelling of one of cervical lymph nodes; thrombosis of one of cubital veins; blotchy eruption appeared	.....	..	.....	87,400	19.5	14.5	5.0	...	7.0	73.5	3.5	70.0	...	...
11/30/28	Intense itching over body; Dr. J. Swartz considered rash to be leukemic infiltration of skin	.....	33	2,390,000	147,400	29.0	26.0	3.0	...	2.0	69.0	3.0	66.0	...	...
12/ 4/28	.....	.....	24	1,440,000	.....	18.0	15.0	3.0	...	3.5	78.5	4.5	4.0	...	...
12/12/28	Face edematous; patient slightly irrational	.....	16	1,010,000	88,400	....	....	...	...	....	....	....	....	...	...
12/14/28	Death after stupor; autopsy not obtained	.....	..	.....	.....	....	....	...	...	....	....	....	....	...	...

of the monocytes was oxidase-negative, in spite of the fact that with Wright's stain large numbers of lilac-staining granules were present in the cytoplasm.

Supravital smears were made daily and showed large numbers of histiocytes and monocytes identically as described in the first case.

Biopsy of the bone-marrow (sternum) was made on May 20. Smears and sections were examined and showed marked crowding of the marrow with primitive cells; 76 per cent of these were oxidase-negative, 1.7 per cent oxidase doubtful and 22.3 per cent oxidase-positive. The oxidase-positive cells included 21.3 per cent of myeloblasts, 0.3 per cent of polymorphonuclear cells and 0.7 per cent of myelocytes. Most of the oxidase-negative cells, which were extremely large, were seen by Wright's stain to be the typical hemohistioblasts of Ferrata with a characteristic spongy nucleus and irregular pale blue-staining cytoplasm.

TABLE 2.—*Blood Picture of Patient in Case 2*

	5/18/30	5/19/30	5/20	5/21	5/22	5/23 a.m.	5/23 p.m.
Hemoglobin	55			44			
Red blood cells	3,720,000	3,670,000		2,800,000			
Platelets		148,000					
Reticulocytes		0.2					
White blood cells	17,200	13,300		21,700	51,800	68,800	124,000
Polymorphonuclears	15.6	33.0	27.5	22.5	11.2	6.0	
Mature	4.0	4.5	2.5	5.0	1.6	2.0	
Band	1.6	1.5	2.0	3.5	2.4	1.2	
Young							
Myelocytes							
Premyelocytes							
Myeloblasts	10.0	27.0	23.0	14.0	7.2	2.8	
Lymphocytes	54.8	47.5	28.0	23.5	4.4	7.2	
Small	32.4	22.0	4.0				
Large	20.4	25.0	24.0				
Plasma		0.5					
Rieder	2.0						
Monocytes	29.6	19.5	44.5	54.0	84.4	86.8	
Ordinary	29.6	19.0	25.0	45.0	77.6	86.4	
Histiocytes		0.5	19.5	9.0	6.8	0.4	

In view of the rapid course, the blood picture and the extreme crowding of the bone-marrow with primitive cells, the diagnosis of acute leukemia was justified. The absence of myelocytes, the constantly increasing number of monocytes and histiocytes (checked by supravital and oxidase staining), the observations in the biopsy of the bone-marrow all served to establish the diagnosis of monocytic (histiocytic) leukemia as against that of myelogenous leukemia.

The patient became rapidly worse. The temperature rose to 105 F., and on May 23, six days after admission, and about ten weeks after the onset of the illness, he died. Permission for autopsy was not obtained; however, bits of muscle and bone-marrow from the sternum were procured. The sections showed crowding of the blood vessels with large mononuclear cells, with some infiltration into the skin and muscle tissue. Bone-marrow showed almost the same observations as in the biopsy specimen, except that more histiocytes and fewer myeloblasts were present.

REVIEW OF THE LITERATURE

Until Reschad and Schilling-Torgau [1] reported their case in 1913, only two types of leukemia were known: lymphatic and myelogenous. Even as late as 1905, grave doubt existed in the minds of some observers as to the presence of even two types of leukemia. Pinkus,[7] in 1905, said that "the definition of acute lymphatic leukemia comprehends all the acute leukemia cases so far known. There is no case described without prejudice which shows other than a lymphatic blood-picture or manifests its principal change in any blood-making tissue other than the lymphatic." In Nothnagel's "Encyclopedia of Practical Medicine," in which the foregoing article was written, there is no description of acute myelogenous leukemia, though the chronic form is mentioned.

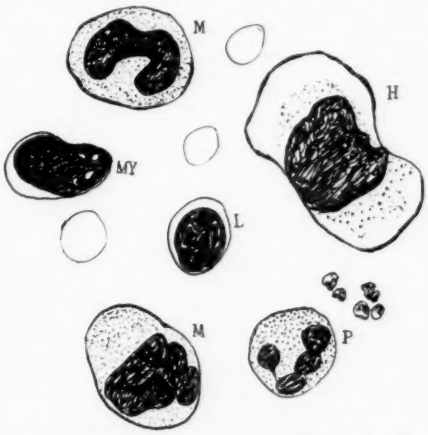

Fig. 1.—These cells are sketched chiefly for purposes of differential diagnosis. Except for the myeloblast (*MY*) they were seen in one oil immersion field on Oct. 27, 1928. The cells were outlined with a camera lucida; × 1,500. Two typical monocytes (*M*), a typical histiocyte (*H*) with a spongy nucleus and characteristic arrangement of granules, a lymphocyte (*L*) with thick chromatin masses composing the nucleus, a myeloblast (*MY*) with very fine nuclear meshwork and nucleoli and a polymorphonuclear cell (*P*) are seen. For further differential points see text.

Since that time, this conception has been almost completely reversed, so that the tendency is now to classify most of the cases of acute leukemia as myelogenous. The possibility is present that some of the cases of acute leukemia classified as lymphatic or myelogenous or unclassified were in reality monocytic in type. The literature will be reviewed briefly in table 3.

7. Pinkus, F.: Acute Lymphatic Leukemia, in Nothnagel: Encyclopedia of Practical Medicine (American Edition), Philadelphia, W. B. Saunders Company, 1905, p. 544.

TABLE 3.—*Review of the Literature*

Author	Date of Case Report		Sex	Age	Duration of Disease	White Blood Cells	Percentage of Monocytes	Postmortem Observations and Comment
Reschad and Schilling-Torgau: München. med. Wchnschr. **60**: 198 (Sept. 9) 1913	1913		M	33	8½ weeks	15,000 to 56,000	72 to 74	Infiltration of skin, bone-marrow, spleen and liver with large mononuclear cells
Fleischmann: Folia haemat. **20**: 19, 1915.....	1915		M	47	6 months	15,600 to 36,000	65 to 58	Infiltration of spleen, lymph nodes, bone-marrow and liver with very large "endothelial" cells; myelocytes also present
Bingel: Deutsche med. Wchnschr. **42**: 1503, 1916..	1916		M	48	9 weeks	4,500 to 16,500	44	Splenic pulp filled with large oxidase-negative cells, not lymphocytes
Rosenthal: M. Clin. North America **4**: 1607, 1921..	1921	(1)	M	5	?	245,000	87.4	
		(2)	Not described					
		(3)	M	34	4 months	600 to 3,000	44	Liver infiltrated with large numbers of mononuclear cells
Komiya and Hayishi: Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **27**: 375, 1921	1921		M	20	5 months	102,000 to 326,000	65 to 79	Intense infiltration of the bone-marrow, splenic pulp, lymph nodes and liver with large mononuclear cells oxidase-negative
Ewald, Frehse and Hennig: Deutsches Arch. f. klin. Med. **138**: 353, 1922	1922	(1)	M	32	24 days	140,000	80 to 87 "Stammzellen" 4.5 to 8	Intense infiltration with large cells ("Stammzellen")
		(2)	M	30	6 weeks	99,600	5 to 7 "Lymphoidocytes" 90	Infiltration with "lymphoidocytes" which were oxidase-positive
		(3)	F	29	?	56,000	60 "Stammzellen" 24	Infiltration with "Stammzellen" and myelocytes
Reitano: Haematologica **3**: 524, 1922.....	1922		..	..	.....	.....	.....	Blood smears of two cases studied; one of Alder (Folia haemat. **29**: 105, 1923); one of Castellino and Ferrata (1914); predominating cells: monocytes and hemohistioblasts of Ferrata

Alder: Folia haemat. **29**: 105, 1923.....	1923 case 7	M	30	Few weeks	100,000	"Granular cells" 40.5	Diagnosis "acute leukemia with marked proliferation and granulation (monoblastic-monocytic leukemia)"
	case 8	M	78	3 months	8,000 to 46,000	"Indented forms" 36.5 "Granular cells" 8.0	Diagnosis "acute leukemia with nuclear polymorphy and granulation (monocytic leukemia)"
	case 12	F	52	14 days	80,000 to 400,000	"Granular cells" 70.0	Diagnosis "myeloblastic leukemia with abnormal nuclear proliferation and cells with fine granulation (monocytic leukemia)"
Ewald: Leukämische Retikuloendotheliose, Deutsches Arch. f. klin. Med. **142**: 222, 1923	1923	M	60	?	15,000	Monocytes 0.2 "Pathologische Stammzellen" 94.75	Infiltration of spleen and bone-marrow with very large cells which contained pseudopods and were intimately associated with the reticulum
Naegeli: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923	1923 (1)	..	..	.....	.....	69.1	Pus in right midlung with rupture into pericardium
	(2)	..	..	.....	.....	12.2 and 1.3	Diagnosis "acute myelogenous leukemia with many monocytes"; myeloid infiltration
	(3)	M	50	.....	4,000	60	Myeloid proliferation in liver, spleen and bone-marrow
Ferrata and Reitano: Haematologica **4**: 385, 1923	1923	Not described					
Hoff: Virchows Arch. f. path. Anat. **261**: 142, 1926	1926 case 4	M	41	3 weeks	2,500 to 5,000	15 to 45	Spleen showed marked increase in monocytes
Merklen and Wolf [2].....	1927, 1928	M	30	3 months	20,000 to 43,000	Monocytes and monoblasts 71 "Ferrata" cells 14	Diffuse infiltration of the reticular tissue in lymph nodes, spleen and bone-marrow (see chapter on pathology)
Ugriumov: Akuter Retikuloendotheliose, Zentralbl. f. allg. Path. u. path. Anat. **42**: 103, 1928	1928	M	30	23 days	36,000	46.5	See chapter on pathology
Hannema: Nederl. tijdschr. v. geneesk. **1**: 2281, 1928	1928	M	11	19 days	107,000	81	Intense infiltration of liver, splenic pulp and lymph nodes
Schwirtschewskaja: Leukämische retikuloendotheliose, Virchows Arch. f. path. Anat. **267**: 456, 1928	1928	M	27	2½ months	6,630	58.7 to 83.3 (many monoblasts)	See chapter on pathology
Hittmair: Folia haemat. **37**: 321, 1928.....	1928	M	63	1 week	38,200	82.7	Liver capillaries and splenic pulp filled with large cells, oxidase-positive
Wyschegorodzowa: Folia haemat. **38**: 355, 1929....	1929	F	38	5 months	2,000 to 23,000	74.5	Infiltration of bone-marrow, spleen, lymph nodes and skin with large mononuclear cells; in the spleen, reticular cells swollen, often with pseudopods, often lying free and containing phagocytosed particles and red blood cells; Kupffer's cells swollen

The following cases of acute monocytic leukemia have been described thus far:[8]

Reschad and Schilling-Torgau	1913	1 case
Fleischmann	1915	1 case
Bingel	1916	1 case
Rosenthal	1921	3 cases
Komiya and Hayishi	1921	1 case
Ewald, Frehse and Hennig	1922	3 cases
Reitano	1922	1 case
Ferrata and Reitano	1923	1 case
Alder	1923	3 cases
Naegeli	1923	3 cases
Hoff	1926	1 case
Merklen and Wolf	1927	1 case
Ugriumov	1928	1 case
Hannema	1928	1 case
Schwirtschewskaja	1928	1 case
Hittmair	1928	1 case
Wyschegorodzowa	1929	1 case

In addition, Merklen and Wolf[2] classed as cases of monocytic leukemia those described by the following authors: Hindenburg (1895), Hertz and Kino (1910), Lino (1924) and Bonnel and Fauqué (1928). Wyschegorodzowa[9] cited a case reported by Barantschik. The case of Hindenburg seems to fit into this group, but Hertz and Kino's case seems to be myeloblastic. The latter three cases could not be checked.

This gives a total of twenty-nine cases, making thirty-one with the present cases. The diagnosis of monocytic leukemia is to be questioned in the following cases: the three cases of Ewald, Frehse and Hennig, which may be cases of myelogenous leukemia with myeloblasts and premyelocytes; the three cases of Naegeli, which are shown by the author himself to be myelogenous leukemia; Hoff's case, which is perhaps one of agranulocytosis, and three of the four cases cited by Merklen and Wolf as monocytic, i. e., those of Hertz and Kino, Lino, and Bonnel and Fauqué. The evidence that these are cases of monocytic leukemia is not entirely conclusive. In addition, the cases of Reitano and of Ferrata and Reitano are not described fully, the reports taking up mainly the morphologic descriptions of the cells. Barantschik's case could not be found. This brings the total of well substantiated, fully described cases of acute monocytic leukemia to eighteen, including the present cases.

8. These cases are reviewed in this article.

9. Wyschegorodzowa, W. D.: Zur Frage der monozytären Leukämie, Folia haemat. **38**:355 (July) 1929.

ANALYSIS OF THE CASES

Clinical Symptoms.—In general, acute monocytic leukemia differs clinically but slightly from the other acute leukemias. The cases occur almost entirely in males, only two (Alder's[10] no. 12 and Wyschegorodzowa's[9] case) occurring in women. The condition appears at any age, from 5 to 78, most of the cases occurring in the age group from 30 to 50.

Etiology.—The etiology is wholly unknown, as in the other leukemias, but several observers have expressed the opinion that the disease is an infection. This opinion is strengthened by the fever, rapid course and almost invariable gingivitis. Some observers, notably Sternberg[11] and Krahn,[12] feel quite strongly that these cases are infections, sufficient irritation of the reticulo-endothelial system having taken place to cause a marked monocytosis. This, to be sure, does not explain the proliferative character of the lesions and the 100 per cent mortality. Blood cultures have been taken in several cases, with negative results.

Onset.—The onset is gradual, usually with fatigue or swollen gums, but at times is acute, with high fever (Ugriumov;[13] Hannema;[14] Alder,[10] case 12). The disease progresses fairly rapidly when the first symptoms appear; the gums become more and more swollen, often ulcerate and at times become gangrenous; fever becomes sustained, and pallor develops. At the first examination, pallor is usually pronounced. The gums are found to be necrotic and swollen. There may or may not be slight glandular enlargement. The liver is usually slightly enlarged, and the spleen is almost always felt below the costal margin. Petechial spots are common, and bleeding is often pronounced. The disease lasts from two weeks to six months, ten weeks being the average time; death occurs either in coma or after repeated bleeding.

Diagnosis.—The diagnosis is made only by morphologic examination of the blood. This shows some degree of secondary anemia, usually marked, the hemoglobin becoming as low as 14 per cent, and the red blood cell count as low as 900,000 per cubic millimeter. The white blood cell count is almost always elevated, though an occasional case is

10. Alder, A.: Ueber abnorme Zellformen und ihre Häufigkeit bei akuter Myelose, Folia haemat. **29**:105 (July) 1923.

11. Sternberg, C.: Akute Leukämie, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 1, p. 76.

12. Krahn, H.: Retikuloendotheliale Reaktion oder "Retikuloendotheliose" (3. Leukämieform?), Deutsches Arch. f. klin. Med. **152**:179 (Aug.) 1926.

13. Ugriumov, B.: Ein Fall von akuter Retikuloendotheliose, Zentralbl. f. allg. Path. u. path. Anat. **42**:103, 1928.

14. Hannema, L. S.: Geval van monocyten leucämie, Nederl. tijdschr. v. geneesk. **1**:2281 (May 5) 1928.

"aleukemic" (Rosenthal,[15] case 2; Schwirtschewskaja,[16] at onset). The average white blood cell count seems to be somewhat lower than in the other two types of acute leukemia, ranging usually from 15,000 to 45,000 per cubic millimeter. Occasionally the white blood cell count reaches very high limits, being 400,000 in one of Alder's cases.[10]

The differential count of the white blood cells ranks first in diagnostic significance. Instead of a marked increase in myelocytes, myeloblasts, lymphocytes or lymphoblasts, there is a marked preponderance (usually from 70 to 90 per cent) of large cells. These are of two varieties: The first type is the ordinary monocyte seen in normal blood pictures. The second type, which is found in greater and greater numbers as the

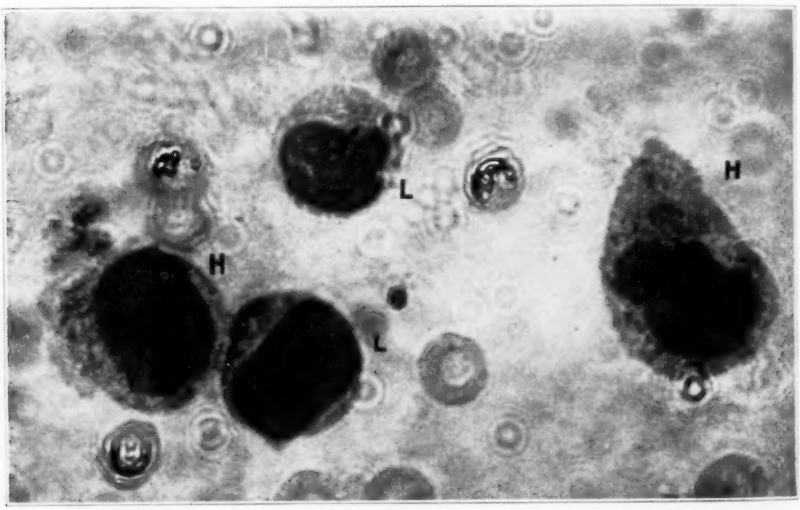

Fig. 2.—Photomicrograph; oil immersion lens; × 1,500; Wright's stain, Oct. 24, 1929. Two histiocytes (*H*) and two lymphocytes (*L*) are shown. Note the faint pseudopods projecting from the histiocyte on the left.

disease progresses, is the histiocyte, the probable forerunner of the monocyte. By Merklen and Wolf,[2] these cells are called monoblasts; by Ferrata and Reitano,[17] hemohistioblasts; by Sabin,[18] clasmatocytes.

15. Rosenthal, N.: Some Atypical Cases of Leukemia, M. Clin. North America **4**:1607 (March) 1921.

16. Schwirtschewskaja, B.: Ueber leukämische Retikuloendotheliose, Virchows Arch. f. path. Anat. **267**:456, 1928.

17. Ferrata, A., and Reitano, D.: Sindromi istiocitemiche (emoistoblastische), Haematologica **4**:385, 1923.

18. Sabin, F.; Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, Carnegie Inst. Contrib. Embryol. **16**:125, 1925.

Maximow [19] finally adopted the term histiocyte, after having called them "resting-wandering cells" for years. A description of these cells will be found in the case report.

The diagnosis of monocytic leukemia rests clinically on the correct diagnosis of the cell known as the monocyte (the endothelial leukocyte of Mallory;[20] the large mononuclear cell of the older authors; the transitional cell of Ehrlich [21]). The diagnosis is ordinarily made without difficulty in a stained preparation. The oxidase reaction is helpful in certain cases as a means of differentiating these cells from lymphocytes and from the myeloid cells.

Supravital staining gives clearcut differentiating points. The monocyte is to be distingushed from the large lymphocyte, the myeloblast, the premyelocyte (and at times the myelocyte) and the polymorphonuclear cell. For convenience, the differentiating points were grouped in tabular form (table 4), the starred items representing the most important factors.

In considering the differential diagnosis, one must separate these cases from acute infections with monocytosis, from acute leukemias of other types and from agranulocytosis. Obviously the progress of the condition and the appearance of large numbers of histiocytes will in time separate the case from one of benign monocytosis. The differential diagnosis from acute leukemias of other types must be made by considering carefully the cell type from the criteria outlined. To differentiate from agranulocytosis becomes at times difficult if the case is of the "aleukemic" variety. The typical picture of agranulocytosis is easy to recognize, but those cases in which symptoms are prolonged may well be difficult to separate from monocytic leukemia. The absolute number of monocytes is to be considered, and histiocytes are to be searched for. In monocytic leukemia there is never complete disappearance of granular cells, whereas in agranulocytosis this is almost always the rule.

PATHOLOGY

Descriptions of postmortem examinations in the foregoing cases of monocytic leukemia are given in eleven instances. The most detailed descriptions are given by Ewald, Ugriumov, Schwirtschewskaja, Wyschegorodzowa and Merklen and Wolf. The lymph nodes, spleen and liver are always slightly enlarged. The normal architecture of the lymph nodes and spleen is effaced by the intense proliferation and infiltration of large mononuclear cells. There is marked infiltration

19. Maximow, A.: Les rélations des cellules sanguines avec le tissu conjonctif et avec l'endothélium, Ann. d'anat. path. **4**:701, 1927.

20. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1923.

21. Ehrlich, P., and Lazarus, A.: Die Anaemie, Vienna, Alfred Hölder, 1909.

also in the bone-marrow and usually in the sinusoids of the liver. Most interesting descriptions showing the direct association between the proliferative reticulo-endothelial cells and the leukemic cells are given by several authors. Ewald described the splenic pulp as filled with large cells, the nuclei being slightly indented; pseudopods, apparently associated with the reticulum cells, were frequently seen. Ugriumov described the mesenteric lymph nodes as markedly enlarged and reddened, the spleen and liver being much enlarged. The splenic pulp and

TABLE 4.—*Differentiating Points Between the Cells*

	Monocyte	Large Lymphocyte	Myeloblast	Premyelocyte	Polymorphonuclear
Size	10-20 microns	10-15 microns	6-15 microns	10-20 microns	10-15 microns
Shape	Oval	Elongated oval	Round to oval	Round to oval	Round
Pseudopods	Fairly common	Rare	Little tags at times	None	None
Cytoplasm:					
Color	Grayish-blue*	Sky-blue	Ultramarine blue	Ultramarine blue verging to pink	Pink
Granules	Innumerable; very fine;* azure	Large, azure in 10% of cells	Absent	Few, large, blue, red or violet	Many, large, blue, red or violet
Vacuoles	Rare	None	None	None	None
Nucleus:					
Size	Relatively large	Eccentric, ½ size of cell	Fills almost entire cell	Large	Variable
Shape	Usually reniform*	Usually round	Oval, at times, indented	Round	Polymorphous
Size of chromatin	Fine network*	Thick, block-like masses	Extremely fine meshwork	Coarse, linear	Coarse, linear
Nucleoli	Absent*	Absent	1 to 5 in each cell	Occasional	None
Oxidase reaction	Slightly positive*	Negative	Usually positive	Positive	Positive
Vital staining	Pseudopods, active movement*	Nucleus moves, rest of cell does not	No motion	No motion	Granules move and push cell membrane out

* The asterisk marks the most important factors in the differentiation.

liver capillaries were full of the large mononuclear cells. The Kupffer or stellate cells of the liver capillaries seemed to be increased in number and often contained red blood cells. The bone-marrow showed these cells in islands. Schwirtschewskaja described the sinuses of the splenic pulp distended with these large cells. In many places the endothelial cells were seen to project out into the lumina of the blood vessels. Pseudopods were common. The reticulo-endothelial system in the spleen, lymph nodes, bone-marrow and liver showed marked hyperplasia. Merklen and Wolf described a diffuse proliferation of the reticular tissue of the lymph nodes, spleen and bone-marrow. The splenic sinusoids showed hyperplasia of the endothelial tissue, and

there was a monocytoid metaplasia of the bone-marrow. The Kupffer cells of the liver showed nothing abnormal. There is thus seen to be constant infiltration of the spleen, lymph nodes, bone-marrow and liver and at times direct evidences of proliferation of the reticulo-endothelial system. This system bears further description.

THE RETICULO-ENDOTHELIAL SYSTEM

A vast literature on the reticulo-endothelial system has accumulated, especially in the last few years. For the most complete reviews, the reader is referred to the articles of Maximow [19] and Bloom [22] and to the "Handbuch der Krankheiten des Blutes und der blutbildenden Organe," volume *2*, articles by Aschoff and Schittenhelm.

Suffice it to say that scattered over the body in various organs and in intimate association with fibroblasts are certain large cells. In 1899, Ranvier [23] described these tissue cells as clasmatocytes; Evans [24] termed them macrophages; Maximow,[25] in 1906, called them resting-wandering cells, but felt, in 1927,[19] that Kiyono's [26] term "histiocyte," though not descriptive, was short and to be preferred, because it had been universally adopted. These histiocytes were to be found scattered in the stroma of the lymph nodes, bone-marrow, spleen and intestine and lining the sinusoids of the spleen, liver, lymph nodes and bone-marrow. In the stroma they seemed to form a reticulum or network and were therefore called "reticular" cells; if they lined the sinusoids, they were called "endothelial" cells. (Maximow objected to the latter, because he felt that it was the same cell whether it helped to form a reticulum or to line a blood vessel. He felt that real endothelial cells were completely differentiated and did not have hematopoietic powers at any time.)

These cells were characterized by certain functional properties: they might under the appropriate stimulus act as hemocytoblasts and thus give rise to other cells; under the influence of certain irritations, they might mobilize and be transformed to free cells which were very phagocytic. These phagocytic qualities could not be regarded as evidence of their inclusion in a "system." However, on the introduction of vital dyes by Ehrlich, it was found by Ribbert,[27] in 1904, working

22. Bloom, W.: The Origin and Nature of the Monocyte, Folia haemat. **37**:1 (Oct.) 1928.

23. Ranvier, L.: Des clasmatocytes, Arch. d'anat. micr. **3**:123, 1899.

24. Evans, H. M.: The Macrophages of Mammals, Am. J. Physiol. **37**:243, 1915.

25. Maximow, A.: Untersuchungen über Blut und Bindegewebe, Arch. f. mikr. Anat. **73**:444, 1909.

26. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914.

27. Ribbert, H.: Die Abscheidung intravenös injizierten gelösten Karmins in den Geweben, Ztschr. f. allg. Physiol. **4**:201, 1904.

with lithium carmine, and by Goldmann,[28] in 1909, working with pyrrhol blue, that these histioid cells had the power of taking up dyes and other substances. This work was carried on by Tschachin,[29] who used various dyes, and was finally consummated by the most complete work of Aschoff and Kiyono,[26] in 1914. Kiyono[30] carried on this work in his own laboratory in Japan.

By the use of these dyes, it was possible to pick out a group or "system" of cells which had been shown before to be alike morphologi-

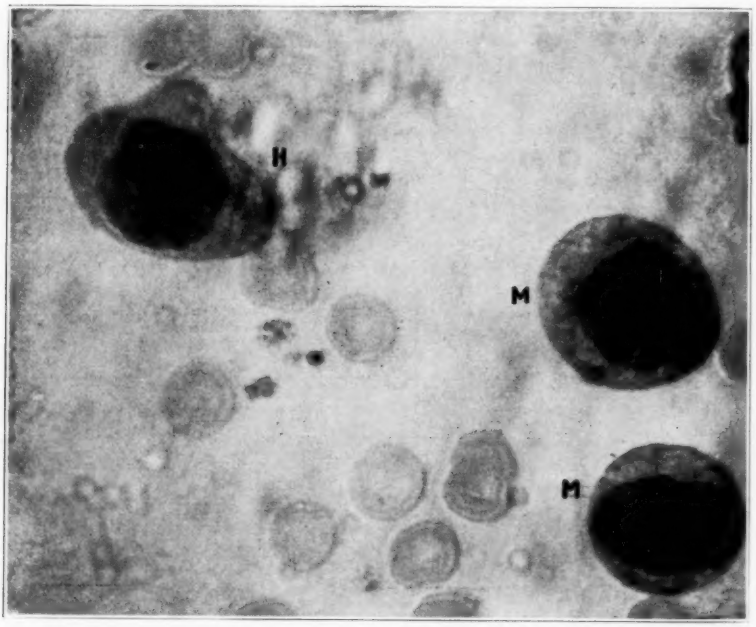

Fig. 3.—Photomicrograph: oil immersion lens: × 1,500; Wright's stain. The cell on the left is a typical histiocyte (*H*) with spongy nucleus and a pseudopod. The two cells on the right represent probably young monocytes (*M*), the nucleus being not yet indented.

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28. Goldmann, E. E.: Die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Farbung," Beitr. z. klin. Chir. **64**:192, 1909.

29. Tschachin, S.: Ueber die "ruhenden Wanderzellen" und ihre Beziehungen zu den anderen Zellformen des Bindesgewebes und zu den Lymphozyten, Folia haemat. **17**:318, 1913.

30. Kiyono, K., and Nakanoin, T.: Weitere Untersuchungen über die histiozytären Zellen, Acta scholae med. univ. imp. Kioto **3**:55, 1919-1920.

cally and culturally, and which now were seen to be functionally active in the storage or phagocytosis of dyes. These cells, functionally similar, were thus elevated to a "system" by Aschoff and his co-workers, and since they occurred in the reticulum of various organs (reticular cells) and lined sinusoids in the same organs (endothelial cells) the system was called "reticulo-endothelial."

During the course of the last fifteen years, other methods of study have demonstrated the functional identity of the cells of this system. It was found that the histiocytes had the power of fat storage, and in the marked lipoidemia which often accompanies diabetes mellitus, these cells were found to be filled with fat (Schöndorff,[31] Schultze[32]). Gaucher's disease was found to be an abnormal storage in the reticulo-endothelial system of a peculiar lipoidal material, probably kerasin.[33] The system has a great capacity for the storage of cholesterol and lipoid-protein mixtures (Chalatow[34]) and for casein (Kuczynski[35]). Niemann's disease represents probably a pathologic storage of cholesterol (Niemann,[36] Bloom[37]). Xanthomatosis is shown by Rowland[38] to be due to infiltration of the reticulo-endothelial system with lipoid substances. Hodgkin's disease is considered by several authors, including Piney,[39] to be a reticulo-endotheliosis. Indeed the conception of reticulo-endotheliosis, an overgrowth of the reticulo-endothelial system, has gained a great deal of favor in recent years.

Using this classification, monocytic leukemia is to be regarded as leukemic reticulo-endotheliosis; there is also aleukemic reticulo-endo-

31. Schöndorff, W.: Ueber die lipoidzellige Hyperpläsie der Milz bei diabetischer Lipoidämie, Virchows Arch. f. path. Anat. **258**:246, 1925.

32. Schultze, W. H.: Ueber grosszellige Hyperpläsie der Milz bei Lipoidaemie (Lipoidzellen-hyperplasie), Verhandl. d. deutsch. path. Gesellsch. **15**:47, 1912.

33. Epstein, E.: Beitrag zur Pathologie der Gaucherschen Krankheit, Virchows Arch. f. path. Anat. **253**:157, 1924.

34. Chalatow, S. S.: Die anistrope Verfettung in Lichte der Pathologie des Stoffwechsels, Jena, Gustav Fischer, 1922.

35. Kuczynski, M. H.: Edwin Goldmanns Untersuchungen über celluläre Vorgänge im Gefolge des Verdauungsprozesses auf Grund nachgelassener Präparate und durch neue Versuche ergänzt, Virchows Arch. f. path. Anat. **239**:185, 1922.

36. Niemann, A.: Ein unbekanntes Krankheitsbild, Jahrb. f. Kinderh. **79**:1, 1914.

37. Bloom, W.: Splenomegaly (Type Gaucher) and Lipoidhistiocytosis (Type Niemann), Am. J. Path. **1**:595, 1925.

38. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928.

39. Piney, A.: Recent Advances in Hematology, Philadelphia, P. Blakiston's Son & Company, 1927, p. 47.

theliosis (Letterer,[40] Goldschmidt and Isaac,[41] Sachs and Wohlwill[42]). Epstein[43] preferred to group all these cases under the title of "histiocytomatoses." He subclassified these into the following types: storage (Gaucher's disease, Niemann's disease, xanthomatosis); infectious proliferative (granulomas) Hodgkin's disease; hyperplastic—aleukemic, leukemic; dysplastic—tumors (reticuloma, endothelioma).

Morphologically, culturally, functionally and pathologically, it can be shown that scattered throughout the body, especially in various organs, are certain large cells, the histiocytes, which can be grouped into one system, the reticulo-endothelium. An acute irreversible proliferation of that system gives the clinical picture called monocytic leukemia.

THE MONOCYTE

It is on the basis that the monocyte is derived directly from the histiocytes composing the reticulo-endothelial system that the conception of monocytic leukemia as a third type of leukemia rests. Almost all are agreed that there are three types of white blood cells, the granular or myeloid, the lymphoid and the monocytic. Since there are these three types of white blood cells, there may be and are three types of leukemias—so Schilling, Rosenthal and other writers on the subject have argued. Some authors have refused to give the monocyte a position independent from the lymphocyte (Weidenreich,[44] Patella,[45] Bloom[22]). Naegeli[46] stands alone in saying that they are bone-marrow cells.

The "monocyte question" is one that occupies a leading place in hematologic discussion. Maximow has long been known as a "unitarian" on the subject, believing that all white blood cells are derived, as has been shown, from the same cell—the hemocytoblast. In his later years, Maximow[19] admitted that in the circulating blood of the normal adult, the monocytes seemed unique, and he therefore felt they

40. Letterer, E.: Aleukämische Retikulose, Frankfurt. Ztschr. f. Path. **30**: 377, 1924.

41. Goldschmidt, E., and Isaac, S.: Endothelhyperplasie als Systemerkrankung des hämatopoetischen Apparats, Deutsches Arch. f. klin. Med. **138**:291, 1921.

42. Sachs, F., and Wohlwill, F.: Systemerkrankungen des retikuloendothelialen Apparats und Lymphogranulomatose, Virchows Arch. f. path. Anat. **264**:640, 1927.

43. Epstein, E.: Die generalisierten Affektionen des histiozytären Zellensystems (Histiozytomatosen), Med. Klin. **21**:1501 (Oct. 2) 1925.

44. Weidenreich, F.: Die Leucozyten und verwandte Zellformen, Wiesbaden, J. F. Bergmann, 1911.

45. Patella, V.: La genesi endoteliale dei monociti, dell forme di passagio e dei cosidetti linfociti del sangue, Hematologica **4**:59, 1923.

46. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

must occupy an autonomous position. The histologic character of the monocyte closely resembles that of the histiocyte. Culturally, they are both actively phagocytic. After intravenous injections of vital dye, certain fixed histiocytes become hypertrophied and desquamate, and are seen in the peripheral blood. According to Maximow, histiocytes never get into the circulating blood, but monocytes are formed directly from them by proliferation in the spleen, liver, bone-marrow and lymph nodes. Monocytes may thus be considered a connecting link between the blood and the lining tissue.

This monophyletic or unitarian conception differs but little from the polyphyletic, the chief exponents of which are Schilling [47] in Germany,

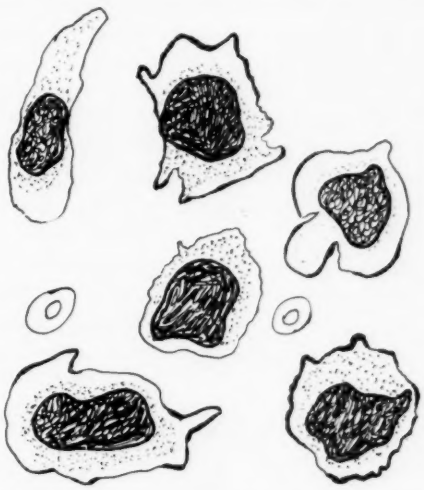

Fig. 4.—Sketches of representative histiocytes (× 1,500) seen on Dec. 4, 1928. The large size, the polymorphism, the irregular cytoplasmic borders representing a very active cell, the spongy nucleus and the characteristic perinuclear arrangement of the granules are shown.

Ferrata [4] in Italy, Merklen and Wolf [48] in France and Kiyono [39] in Japan. The monophyletic school says that all the blood cells are derived from a primitive blood cell, to which all are agreed. The polyphyletic or trinitarian school says that there is differentiation in the embryo into three types of blood-forming tissue—myeloid, lymphatic and reticulo-endothelial (which most of the unitarians readily admit)—but that this differentiation is irreversible. In other words, there can be no

47. Schilling, V.: Das Blutbild und seine klinische Verwertung, ed. 2, Jena, Gustav Fischer, 1922.

48. Merklen, M., and Wolf, M.: Le monocyte, Ann. d'anat. path. **4**:621, 1927.

transitions between monocytes and lymphocytes, and monocytes and lymphocytes can always be separated easily. The unitarians, however, say that transitions between lymphocytes and monocytes can be seen, and some of them maintain that lymphocytes cannot be distinguished clearly from monocytes (Downey,[49] Weidenreich,[44] Patella,[45] Bloom [22]).

The dualistic school—Naegeli—has no supporters. Ehrlich [21] thought the monocytes to be transitions between the granular cells and the lymphoid cells, but this view has long since been discarded.

The concensus at the present time is that the monocyte is derived directly from the histiocytes which form the reticulo-endothelial system. This opinion is based on: (1) morphologic characteristics: transitions between histiocytes and monocytes are clearly seen both under normal and under pathologic conditions (as in leukemias, malaria, etc.); (2) cultural characteristics: tissue cultures by Maximow, cell cultures by Maximow and others; (3) bacteriologic investigations: production of monocytosis by injection of *B. monocytogenes* (Murray,[50] Lang[51]); examination of the animals after death; studies by this method combined with vital staining; (4) vital staining methods: intravital staining in the animal; supravital staining.

CONCEPTIONS OF MONOCYTIC LEUKEMIA

The medical world has been disinclined to accept this third form of leukemia, the monocytic. This has been due in part, of course, to the fact that there is as yet no unified conception concerning the nature or the derivation of the monocyte. In most part, acceptance has probably been delayed because the conception of only two types of leukemia —myelogenous and lymphatic—has become so firmly ingrained that a third seems unbelievable. Again, overgrowth of the histiocytic tissue (reticulo-endothelial system) in the bone-marrow must necessarily bring with it more or less overgrowth of the closely adjacent myeloid tissue, so that if a monocytic leukemia lasts long enough, it becomes a mixed leukemia.

What are the expressions of the various writers on the subject of monocytic leukemia? In 1925, Hirschfeld [52] wrote (on the basis of the first three reported cases): "Because of the few cases of monocytic leukemia, the relationship to the other types of leukemia is obscure.

49. Downey, H.: The Occurrence and Significance of the "Myeloblast" Under Normal and Pathological Conditions, Arch. Int. Med. **33**:301 (March) 1924.

50. Murray, E. G. D.; Webb, R. A., and Swann, M. B. R.: Disease of Rabbits Characterized by Large Mononuclear Leucocytosis, Caused by Hitherto Undescribed Bacillus, Bacterium Monocytogenes, J. Path. & Bact. **29**:407 (Oct.) 1926.

51. Lang, F. J.: Zur Monozytenfrage, Folia haemat. **36**:383, 1928.

52. Hirschfeld, H.: Leukemia, in Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 1, p. 411.

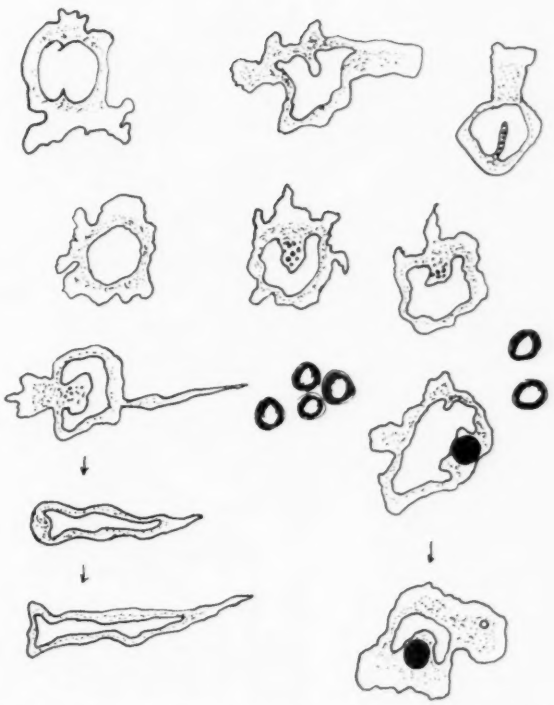

Fig. 5.—Drawings made from living white blood cells on Nov. 27, 1928. Neutral red, 20 drops (of stock solution) and Janus green, 5 drops (of stock solution) in 2 cc. of absolute alcohol was used as stain; the preparation was kept at 37.5 C. in a hot box. Histiocytes and monocytes are to be seen, the dividing line between the two being difficult to make. Those cells with marked indentation of the nucleus and clustering of neutral red granules in the bend of the nucleus are probably monocytes. The rapid changes in size and shape of these cells are shown in the lower drawings. These changes took place within from two to three minutes. The histiocyte on the right has a red blood cell inclusion and changed its size very rapidly, apparently in attempts to digest the red cell. A small vacuole appeared in this histiocyte after two minutes. Several red blood cells are pictured for comparison in size. Note the tendency of the neutral red granules to remain near the nucleus, their entrance into the pseudopods being delayed a varying length of time. The mitochondria, which take the Janus green, are seen as delicate filaments interspersed among the granules. Oil immersion, Leitz, 1/12 objective, no. 10 eyepiece; × 1,000.

The appearance of myeloid elements in the blood in Fleischmann's and Hirschfeld's case as well as the marked degree of myeloid degeneration in Fleischmann's case make one think that this is an ordinary myelogenous leukemia with a one-sided differentiation into monocytes."

Naegeli,[46] writing in the last edition (1923) of his textbook, considered (also on the basis of the first three cases and of three questionable cases he had seen) that "so-called monocytic leukemia was a temporary variant of myelogenous leukemia into which it passes unless death intervenes."

Piney,[39] writing in 1927, said that the "evidence seems to be all in favor of the conception of monocytic leukemia belonging to the group of myelosis, and not being a special form of leucosis (leukemia) depending upon proliferation of the cells of a third hematopoietic system."

Schilling-Torgau,[1] in the original article and in his textbook, said that there is no doubt but that there is a third type of leukemia just as there are three types of white blood cells. Ferrata and Reitano,[17] in discussing the appearance of histiocytes in leukemia and in other conditions, brought out the fact of the presence of large numbers of histiocytes in monocytic leukemia, which they recognized as an entity. Ferrata and Reitano [17] expressed the belief that there is an acute histiocythemic syndrome.

Krahn,[12] in a critical analysis of "reticulo-endotheliosis" in which he discussed a few of the reported cases of monocytic leukemia, came to the conclusion that reticulo-endotheliosis is merely a reaction to infection. He said that the whole question of the monocyte is so uncertain that the conception of monocytic leukemia as a third entity is not to be considered. This analysis appears deficient in that only a few cases are mentioned, and these are doubtful. Consideration of acute monocytic leukemia as an infection may perhaps be correct, but the other acute leukemias appear to be just as infectious, so that it would be advisable, if Krahn were to be followed, to drop the entire conception of acute leukemia.

Fleischmann,[53] in 1915, thought that his case was at first monocytic, later becoming mixed monocytic-myelogenous. Bingel,[54] in 1916, observed that if these cases were seen more frequently, the existence of a third form of leukemia would thereby be proved. Rosenthal,[15] in 1921, strongly favored the third form of leukemia based on the third type of white blood cell, the monocyte. Ewald, Frehse and Hennig,[55]

53. Fleischmann, P.: Der zweite Fall von Monozytenleukämie, Folia haemat. **20**:19 (Oct. 1) 1915.

54. Bingel: Monozytenleukämie? Deutsche med. Wchnschr. **42**:1503 (Dec. 7) 1916.

55. Ewald, Frehse and Hennig: Akute Monozyten- und Stammzellen Leukämien, Deutsches Arch. f. klin. Med. **138**:353 (Feb.) 1922.

in 1922, in discussing "Stammzellenleukämie," concluded that a specific irritant may bring about marked cytogenesis of the mother cells of the hematopoietic tissue and thus produce a leukemia in which are present "Stammzellen," the forerunners of the monocytes. Ewald,[56] in 1923, thought that acute reticulo-endotheliosis was a third type of leukemia in which the primordial or "Stammzellen" were involved.

Komiya and Hayishi,[57] in 1921, thought definitely that there was a third type of leukemia, as did Hoff [58] in 1926. On the other hand, Alder,[10] in 1923, thought that "the expression monocytic leukemia is often incorrectly used and without foundation. True monocytic leukemia, as the observation of Reschad and Schilling is extremely rare." He said, too, that "it is advisable to let the idea of monocytic leukemia go or turn to it with reserve. . . ." All the authors who described cases in 1928 are definite as to the third type of leukemia, which most of them called reticulo-endotheliosis (Ugriumov,[13] Schwirtschewskaja,[16] Hittmair [59]). The latter two authors discussed the various types of reticulo-endotheliosis—leukemic, aleukemic, etc. Merklen and Wolf,[2] whose work on monocytic leukemia has been exhaustive, distinguished the three types of leukemia.

It is probably true that the more "acute" a case of leukemia is, the more primitive does the predominating cell type become. Since the most primitive cell is the hemocytoblast (hemohistioblast, histiocyte, "Stammzell"), these cells should appear in the most acute cases of leukemia. Since these cells may potentially produce all the other white blood cells, it may well be that certain cases of acute leukemia merge one into the other. Thus, monocytic leukemia may be related more or less closely to myelogenous leukemia. It is felt, however, that certain cases of monocytic leukemia are "pure," with intense proliferation of the histiocytic system and but little or no involvement of the other systems or tendency to develop into the other forms of leukemia.

SUMMARY AND CONCLUSIONS

Two cases are presented in which the diagnosis of acute monocytic leukemia was made. With these cases, there have been eighteen well substantiated instances of the disease since the first report in 1913.

56. Ewald, O.: Die leukämische Retikuloendotheliose, Deutsches Arch. f. klin. Med. **142**:222, 1923.

57. Komiya, E., and Hayishi, T.: Ueber die Monozyten- und Monozytenleukämie Frage beurteilt von einem jüngst von uns beobachteten Fall, Mitt. a. d. Med. Fakult. d. k. Univ. zu Tokyo **27**:375 (Nov.) 1921.

58. Hoff, F.: Beiträge zur Pathologie der Blutkrankheiten, Virchows Arch. f. path. Anat. **261**:142, 1926.

59. Hittmair, A.: Zur Frage der sogenannten Retikuloendotheliosen, Folia haemat. **37**:321 (Dec.) 1928.

Supravital staining of the blood served to confirm the diagnosis of the type cell, the histiocyte.

A review of the literature on the subject is presented. Since the conception of the third form of leukemia is linked intimately with the studies on the reticulo-endothelial system and on the monocyte, these subjects are discussed in some detail.

The monocyte appears to be a distinctive cell directly derived from the reticulo-endothelial system. Various disorders of this system have been described: abnormal storage (Gaucher's disease, Niemann-Pick's disease, xanthomatosis); irritations due to infections (monocytosis); tumor growth (endothelioma, reticuloma), and proliferation (leukemia). The proliferative lesions—reticulo-endotheliosis—may be leukemic or aleukemic. Leukemic proliferation results in the clinical entity known as monocytic leukemia.

It is thought, therefore, that the third type of leukemia should be added to the two accepted types. Though apparently much rarer than either myelogenous or lymphatic leukemia, clearcut cases of monocytic leukemia at times appear and should not escape recognition.

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